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PARA-AMINOBENZOIC ACID IN TREATMENT OF ROCKY MOUNTAIN SPOTTED FEVER

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ALTHOUGH there have been several reports in the recent literature concerning the use of para-aminobenzoic acid in the treatment of rickettsial diseases, the number of reported cases of Rocky Mountain spotted fever in which this drug was used is comparatively small. The first case was reported by Rose, Duane and Fischel.[1] Then followed articles by Maroney and associates,[2] Ross and Smith,[3] Flinn and associates,[4] and Hendricks and Peters.[5] Experimentally, the drug has been proved to be rickettsia static,[6] and it has been effective clinically in cases of epidemic typhus,[7] endemic (murine) typhus[8] and tsutsugamushi fever.[9]

The value of para-aminobenzoic acid in the treatment of Rocky Mountain spotted fever seems unquestioned. However, the drug has not yet been completely evaluated clinically, and many details regarding its use require clarification. The present study applies particularly to the methods of giving the drug, the complications which may arise, and the determination of adequate doses and optimum blood levels; the minimal period of treatment required to prevent recurrence must also be considered, as well as how late in the disease the drug may be effective.

From the Division of Pediatrics, University of Tennessee College of Medicine.

1. Rose, H. M.; Duane, R. B., and Fischel, E. E.: The Treatment of Spotted Fever with Para-Aminobenzoic Acid, J.A.M.A. **129**:1160-1161 (Dev. 22) 1945.

2. Maroney, J. W.; Davis, H. C., and Scott, E. G.: Rocky Mountain Spotted Fever: A Case Treated with *p*-Aminobenzoic Acid, Delaware State M. J. **18**:104-106 (May) 1946.

3. Ross, S., and Smith, P. K.: Rocky Mountain Spotted Fever Treated with Para-Aminobenzoic Acid, Clin. Proc. Child. Hosp. **2**:258-265 (Sept.-Oct.) 1946.

4. Flinn, L. B.; Howard, J. W.; Todd, C. W., and Scott, E. G.: Para-Aminobenzoic Acid Treatment of Rocky Mountain Spotted Fever, J.A.M.A. **132**:911-915 (Dec. 14) 1946.

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(Footnotes continued on next page)

This series comprises 6 cases of Rocky Mountain spotted fever, the total number recorded at John Gaston Hospital since 1940. One case occurred in May 1945 and the other 5 during 1946. Whether the disease is more widespread in this area than has been believed or whether cases of it have not been recognized in the past, we are unable to say. In 2 of the cases presented treatment with para-aminobenzoic acid was not included while in 4 this drug was used. We realize that this group of cases is small; therefore we do not present the 2 "untreated" cases as actual controls but for their relative and comparative values.

REPORT OF CASES

CASE 1.—C. H., a 7 year old white boy, was admitted to the isolation hospital on May 6, 1945, with the complaints of fever, rash and swelling of the eyelids and feet. Fever started one week before admission. On the next day a reddish purple, maculopapular rash appeared, which covered the entire body. No note was made of the original site of the rash or of the pattern of spread. A physician was consulted who diagnosed the condition as a septic sore throat and gave the patient a medicament in the form of tablets. On the day prior to admission, the child's feet began to swell and his eyelids were puffy. He complained also of headache. The child had had measles, whooping cough and chickenpox, and he had been vaccinated against diphtheria and smallpox. The family history was noncontributory.

Physical examination revealed a well developed and well nourished child, with flushed face and circumoral pallor. He lay quietly in bed and appeared dull and lethargic. The rectal temperature was 103.6 F.; the pulse rate was 130 and the respiratory rate 26 per minute. There was a mild nuchal rigidity, with an equivocal Kernig sign.

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6. Greiff, D.; Pinkerton, H., and Moragues, V.: Effect of Enzyme Inhibitors and Activators on the Multiplication of Typhus Rickettsiae: I. Penicillin, Para-Aminobenzoic Acid, Sodium Fluoride and Vitamins of the B Group, J. Exper. Med. **80**:561-574 (Dec.) 1944. Hamilton, H. L.; Plotz, H., and Smadel, J. E.: Effect of Para-Aminobenzoic Acid on the Growth of Typhus Rickettsiae in the Yolk Sac of the Infected Chick Embryo, Proc. Soc. Exper. Biol. & Med. **58**:255-262 (April) 1945. Hamilton, H. L.: Effect of Para-Aminobenzoic Acid on Growth of Rickettsiae and Elementary Bodies, with Observations on Mode of Action, ibid. **59**:220-226 (June) 1945. Murray, E. S.; Zarafonetis, C. J. D., and Snyder, J. C.: Further Report on Effect of Para-Aminobenzoic Acid in Experimental Tsutsugamushi Disease (Scrub Typhus), ibid. **60**:80-84 (Oct.) 1945. Snyder, J. C., and Zarafonetis, C. J. D.: Effects of Para-Aminobenzoic Acid in Experimental Tsutsugamushi Disease (Scrub Typhus), ibid. **60**:115-117 (Oct.) 1945. Anigstein, L., and Bader, M. N.: Para-Aminobenzoic Acid—Its Effectiveness in Spotted Fever in Guinea Pigs, Science **101**:591-592 (June 8) 1945; Antirickettsial Activity of Para-Aminobenzoic Acid. (PABA): Effect of PABA on Experimental Spotted Fever, Texas Rep. Biol. & Med. **4**:260-278, 1946.

7. Yeomans, A.; Murray, E. S.; Zarafonetis, C. J. D., and Ecke, R. S.: The Therapeutic Effect of Para-Aminobenzoic Acid in Louse-Borne Typhus Fever, J.A.M.A. **126**:349-356 (Oct. 7) 1944.

8. Smith, P. K.: The Use of Para-Aminobenzoic Acid in Endemic (Murine) Typhus, J.A.M.A. **131**:1114-1117 (Aug. 3) 1946.

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The throat was severely inflamed. The tongue was deep red. The axillary, cervical and inguinal glands were slightly enlarged. The only other significant observation was a generalized macular and petechial rash, which seemed to be fading, except on the feet where it was still prominent.

Laboratory studies revealed 12.5 Gm. of hemoglobin per hundred cubic centimeters; 4,700,000 erythrocytes and 12,950 leukocytes per cubic millimeter, with 88 per cent polymorphonuclear cells, 10 per cent lymphocytes and 2 per cent large mononuclear forms. The spinal fluid obtained on lumbar puncture was normal, except for 205 mg. of protein per hundred cubic centimeters. A culture of material from the throat was negative for diphtheria organisms. The bleeding time was 2½ minutes and the coagulation time 3 minutes. Cultures of the blood and spinal fluid were negative for organisms. An agglutination series taken on the date of admission gave a negative reaction for typhoid, brucellosis, tularemia and Proteus vulgaris OX_{19}. Agglutination for heterophil antibodies occurred in a dilution of 1:32. The patch test with tuberculin gave a negative reaction. Routine urinalyses of voided specimens repeatedly showed nothing abnormal.

The spinal puncture was repeated on May 11 and 16. The fluid was still normal on May 11, except for 117 mg. of protein per hundred cubic centimeters. On May 16, 151 cells per cubic millimeter were seen, of which 63 per cent were lymphocytes and 37 per cent polymorphonuclear leukocytes. The sugar and chloride concentrations were still within normal limits; the amount of protein was not recorded.

On May 17, the reaction to the Weil-Felix agglutination test was reported positive in a titer of 1:640 for P. vulgaris OX_{19}. The complement fixation test gave a positive reaction in a titer of 1:160 for Rocky Mountain spotted fever.

The child had a septic temperature, with daily peaks of 103 to 104 F., and was lethargic, irritable and, sometimes, delirious.

Therapy consisted of administration of sulfadiazine until May 11. On this date the sulfonamide compound was discontinued, and the child was given penicillin, which was administered until the date of his discharge from the hospital.

On May 15 the temperature began gradually to subside. The child became less irritable and more cooperative, and the sensorium cleared. On May 22, the day of discharge from the hospital, he was completely asymptomatic and his rash had disappeared.

CASE 2.—B. K., a white boy 10 years of age, weighing 70 pounds (31.8 Kg.), was admitted to the isolation hospital on June 2, 1946. Six days prior to admission the child had complained of headache, nausea and general malaise. Two days later he had a rigor and chill, followed by an extreme rise in temperature. Vomiting occurred after eating. The next morning a rash was noted on the cheeks and on one extremity. It spread rapidly to cover the entire body. He was given 200,000 units of penicillin by another physician; but the temperature remained high and the child complained of pain and soreness in his extremities. No history of a tick bite was obtained. However, it was reported that he had been playing about a lumber factory which was tick infested; he complained of a bite on his left foot from an insect which he called a bee. Whether this insect was a tick or not is conjectural.

The past history was irrelevant, and the family history contributed the information that one grandfather had died of tuberculosis and that the father was being treated for syphilis of the central nervous system.

Physical examination on admission to the hospital revealed an acutely ill child, who was well developed and well nourished. The rectal temperature was 104 F., the pulse rate 120, and the respiratory rate 26. There was a generalized maculopapular rash, which was more pronounced on the arms, legs, back and buttocks, and which blanched on pressure. Some petechiae were present on the forearms. The only other observations were mild conjunctivitis, palpable spleen and hyperactivity of the deep reflexes.

Blood cultures and cultures of the stool yielded no organisms. An agglutination series gave a negative reaction for typhoid, tularemia, P. vulgaris OX_{19} and brucellosis. Routine urinalyses showed nothing abnormal, and the Kahn test for syphilis gave a negative reaction. The hemoglobin content was 12 Gm. per hundred cubic centimeters; the erythrocyte count was 4,030,000 and the leukocyte count 7,200, per cubic millimeter, with 80 per cent polymorphonuclear and 20 per cent mononuclear cells.

Penicillin therapy, 20,000 units every three hours, was reinstituted at the time of admission. However, a diurnal remittent fever ensued, and the child became delirious and had hallucinations at its height. The range of rectal temperature was 105.5 to 97 F. Epistaxis occurred several times.

Additional laboratory examinations included a blood smear for the presence of malarial parasites, culture of the urine, which yielded no organisms, and agglutination tests for heterophil antibodies, which gave negative results. The sedimentation rate (Cutler) was 20 mm. in 60 minutes. The total serum protein was 5 Gm. per hundred cubic centimeters on June 12.

Nuchal rigidity, with positive Brudzinski and Kernig signs, developed to some degree on the fourth day in the hospital, but the spinal fluid was normal.

Sulfadiazine, 2 Gm. administered immediately and 0.5 Gm. every four hours thereafter, was started on June 5 and was continued for four days, with no improvement.

Agglutinations with P. vulgaris OX_{19}, repeated on June 10, 12 and 14, reacted in dilutions of 1:640, 1:1,280 and 1:2,560, respectively. The complement fixation test on June 21 was positive in a titer of 1:640 for Rocky Mountain spotted fever and gave no reaction for endemic (murine) typhus. Biopsy of a specimen of skin was reported to show a process consistent with an arterial lesion of rickettsial origin.

An unsuccessful attempt was made to obtain para-aminobenzoic acid. The patient received symptomatic and supportive therapy, including dextrose in isotonic solution of sodium chloride, plasma and blood transfusion.

On the fourteenth day in the hospital, the twentieth day of illness, the temperature began to fall by lysis, and on the twenty-third day of illness, it became and remained normal. The child was asymptomatic when seen in the outpatient clinic on June 28. The rash was still present but had faded.

CASE 3.—W. E., a 6 year old white boy, weighing 45 pounds (20.4 Kg.), was admitted to the isolation hospital on July 1, 1946. His illness began June 24, with headache, elevated temperature, sore throat, generalized aches and pains, extreme malaise and vomiting. The symptoms increased in intensity on the succeeding days, and there were several episodes of nosebleed. On the third day of illness a rash appeared, which became generalized. No note was made of the point of origin or the pattern of spread. The child lived in a rural district where dogs were infested with ticks. On several occasions ticks had been removed from the boy, although it was felt that he had never been bitten.

The past history and the family history were not significant. Physical examination revealed a temperature of 104.6 F., a respiratory rate of 26 and a pulse rate of 126. The patient was irritable and appeared moderately ill. There was a generalized rose-colored, macular rash which was most pronounced on the extremities and involved the palms and soles. The conjunctivas were moderately inflamed. The tonsils were hypertrophied and red. The lungs were normal, but examination of the heart revealed a functional systolic murmur over the precordium, with tachycardia. The liver and spleen were just palpable. The cervical, axillary and inguinal nodes were moderately enlarged and slightly tender. There were no abnormal neurologic signs.

Laboratory studies on admission revealed the following values: 4,150,000 erythrocytes and 10,900 leukocytes per cubic millimeter, with 65 per cent polymorphonuclear cells, 31 per cent lymphocytes and 4 per cent large mononuclear forms. The hemoglobin

concentration was 10.5 Gm. per hundred cubic centimeters. Routine urinalysis of a voided specimen showed it to be normal.

Blood cultures and cultures of the stool revealed no pathogens. An agglutination series taken on July 3 gave a positive reaction for P. vulgaris OX_{19} in a dilution of 1:160. On July 9 a positive reaction for P. vulgaris OX_{19} was obtained in a dilution of 1:640. Biopsy of skin from the calf of the right leg was reported to show a picture consistent with an arterial lesion of rickettsial origin.

The condition was diagnosed as Rocky Mountain spotted fever, and on the second day in the hospital administration of para-aminobenzoic acid was started, with 3 Gm. in 25 cc. of 5 per cent solution of sodium bicarbonate being given every four hours. The following day the temperature began to drop, and on the third day of medication the patient was afebrile and remained so until his discharge on the eleventh day from the hospital. Para-aminobenzoic acid was discontinued on the third afebrile day.

CASE 4.—C. D., a white girl 7 years of age, weighing 46 pounds (20.9 Kg.), was admitted to the isolation hospital on July 10, 1946. The history revealed that ticks had been removed from the patient's body and scalp on several occasions prior to onset of symptoms. The illness began June 30, with fever, headache, and malaise and with some tenderness and rigidity of the neck. On the next day she was taken to a physician, who made a diagnosis of septic sore throat and instituted sulfonamide therapy, which was continued for two days. She seemed to improve temporarily, but on the fourth day of illness she became increasingly drowsy and complained of pain and soreness in her arms and legs. A rash appeared on the extremities and spread centripetally. She became rapidly worse, and on the date of admission to the hospital the patient was listless, drowsy, irrational, disoriented, extremely uncooperative and acutely ill. The past history and family history were noncontributory.

The patient's rectal temperature was 104 F.; the pulse rate was 130, and the respiratory rate was 18. The skin of the entire body, including that of the palms and soles, was covered with a rose-colored, macular rash. The conjunctivas were injected, and both ear drum membranes were mildly hyperemic. The tonsils were enormously enlarged and inflamed and covered with pus-filled follicles. The neck was moderately rigid. The spleen was somewhat enlarged. All superficial lymph nodes were enlarged, but not tender. The abdominal reflexes and the knee and ankle jerks were absent. The left biceps reflex was considered weak.

Laboratory examination of the blood revealed the hemoglobin content to be 11 Gm. per hundred cubic centimeters; the erythrocytes 3,770,000, and the leukocytes 28,800, per cubic millimeter, with 89 per cent polymorphonuclear cells and 11 per cent lymphocytes. The urine contained 4 to 6 sulfonamide crystals, an occasional clump of white cells and a rare blood cell per high power field. The spinal fluid contained a total of 140 cells per cubic millimeter, with 79 per cent lymphocytes, 17 per cent polymorphonuclear leukocytes and 4 per cent erythrocytes. Chemical studies of the spinal fluid revealed levels of 45 mg. for protein, 57 mg. for sugar and 590 mg. for chlorides, per hundred cubic centimeters. Cultures of the blood and spinal fluid yielded no organisms. The blood nonprotein nitrogen level was 30 mg. per hundred cubic centimeters. Weil-Felix agglutination tests with P. vulgaris OX_{19} showed no reaction on July 11 and 14 but reacted positively in a titer of 1:320 on July 16. A biopsy specimen of the skin showed a picture consistent with arterial disease of rickettsial origin.

Para-aminobenzoic acid therapy was started on July 13, and the patient received 3 Gm. every four hours for seven days, with the exception of a thirty-six hour period when she received this dose every two hours. On July 15 she received 10 cc. of human immune globulin U.S.P. by intramuscular injection.

During the first few hours after the administration of para-aminobenzoic acid was started she seemed to improve slightly, but she did not regain full consciousness. On

the second day she seemed much worse, and from this time her course was steadily downward. On July 18 her urine contained 4 to 6 red blood cells per high power field. Urinalysis showed a 3 plus reaction for acetone, a 2 plus reaction for the Benedict reducing substance and a 3 plus reaction for albumin. The para-aminobenzoic acid level of the blood reached 262 mg. per hundred cubic centimeters on this date. She became acidotic, had frequent nosebleeds, vomited dark blood and had melena. She was given transfusions of blood plasma, sixth-molar solution of sodium lactate and isotonic solution of sodium chloride, with no improvement noted. She died on the eleventh day in the hospital.

CASE 5.—B. H., a 9 year old white boy weighing 72 pounds (32.7 Kg.), was admitted to the isolation hospital on July 26, 1946, with complaints of headache and pain in the legs.

The patient had been in excellent health until one week prior to admission, when he began complaining of headache, sore throat and aching muscular pains. A high fever developed. A diagnosis of measles was made, and a sulfonamide compound was prescribed. On the third day of illness a rash appeared on the extremities and later spread to the trunk. Medication with the sulfonamide compound was discontinued, but the rash and fever persisted with the aforementioned symptoms, which increased in severity. The child was constipated; his appetite was poor, and he was nauseated and vomited several times.

The past history and the family history were noncontributory. Numerous ticks were present in the neighborhood, but the child did not remember being bitten.

Physical signs were absent except that the child appeared moderately ill, with a rectal temperature of 102.6 F. and a macular rash over the entire body.

The diagnosis on admission was Rocky Mountain spotted fever. Laboratory examination revealed a hemoglobin concentration of 12 Gm. per hundred cubic centimeters; 4,340,000 erythrocytes, and 8,500 leukocytes, per cubic millimeter, with 50 per cent polymorphonuclear cells, 48 per cent lymphocytes, 1 per cent monocytes and 1 per cent eosinophils. A routine urinalysis of a voided specimen showed nothing abnormal.

The reaction to the Weil-Felix agglutination test with P. vulgaris OX_{19} was positive in a titer of 1:80 on July 29 and in a titer of 1:640 on August 2. The complement fixation test was positive for Rocky Mountain spotted fever.

Therapy was started with para-aminobenzoic acid on the morning after admission. He was given 4 Gm. immediately and 1 or 2 Gm. every two hours for five days. A blood level of 34.4 mg. per hundred cubic centimeters was obtained on July 28. The drug was given in chilled 5 per cent solution of sodium bicarbonate.

Definite clinical improvement was noted in twenty-four hours after institution of therapy, and on the third day the patient was asymptomatic and free of fever.

Difficulty was experienced in getting the child to take the drug. Occasional vomiting occurred, and he complained of abdominal pain. A 1 plus reaction to a reducing substance in the urine was noted on August 1, one day after the drug was discontinued, and a leukocyte count of 5,050 per cubic millimeter was obtained on July 31.

There was a slight secondary rise in temperature which began on the day after the drug was discontinued and persisted for two days, but the patient continued asymptomatic.

CASE 6.—T. B., a white boy 7 years of age who weighed 65 pounds (29.5 Kg.), was admitted to the isolation hospital on Nov. 20, 1946, with presenting symptoms of fever, vomiting and generalized aches and pains. The onset had occurred ten days previously with what appeared to be a common cold, and was followed in four days by vomiting and a sudden rise in temperature. Two days later the child complained of generalized aches and pains, and two days prior to admission he had become hoarse. There were sharp rises in temperature daily, associated with delirium and irrationality. The duration of a generalized rash observed on the child on admission was not known nor was

the pattern of spread. The child lived in a rural district in which ticks were known to be present. The past and family histories were noncontributory.

On physical examination the rectal temperature was 103 F.; the pulse rate was 100, and the respiratory rate was 20. The patient appeared well developed but dehydrated, weak, stuporous and acutely ill. A generalized macular rash was present, which assumed a petechial character over the upper and lower extremities. The neck was flaccid. Examination of the eyes revealed that the fundi were normal. There was moderate infection of the pharynx. The heart and lungs were normal. There was moderate tenderness over the area of the liver and the edge of the organ was palpable. The spleen could not be felt. A few petechiae were present on the scrotum. Laboratory studies on the day of admission to the hospital, November 21, revealed an erythrocyte count of 4,520,000 and a leukocyte count of 17,800, per cubic millimeter, with 90 per cent polymorphonuclear cells and 10 per cent lymphocytes. The hemoglobin concentration was 12 Gm. per hundred cubic centimeters. A specimen of voided urine showed nothing abnormal except a p_H of 4.5. Spinal fluid obtained on admission because of the possibility of meningococcemia was normal, and cultures of the blood and spinal fluid yielded no organisms. An agglutination series was positive for typhoid in a dilution of 1:320 and for P. vulgaris OX_{19} in a dilution of 1:320.

Rickettsial infection was considered in the differential diagnosis, and the sulfonamide drug was withheld. The patient was placed under treatment with penicillin. On November 22 the patient had semisolid, dark brown stools streaked with blood and mucus. Also, the rash assumed a purpuric character over the hands and ankles. The platelet count was 40,000 per cubic millimeter (Rees and Ecker); the bleeding time was 10 minutes and the coagulation time 6½ minutes. The patient had become edematous, more irritable and restless, while the stuporous state had deepened. Hemorrhages were noted in the bulbar conjunctiva.

On the evening of November 22, administration of para-aminobenzoic acid was begun with an immediate dose of 4 Gm. in 25 cc. of 5 per cent solution of sodium bicarbonate and then 2 Gm. every two hours. The drug was later given in 1 ounce (30 cc.) of fruit juice. Blood levels on November 25, 27 and 30 were 70, 84 and 39 mg., per hundred cubic centimeters, respectively. The blood nonprotein nitrogen level was 23 mg. per hundred cubic centimeters on November 25. During this time the child was being given dextrose, plasma and blood by a continuous intravenous infusion.

The temperature began to subside; delirium was clearing, and, though still confused, the patient was more easily aroused after the onset of therapy. On November 26 the patient was able to take breakfast, and, on the following days, the mental picture cleared rapidly. Repeated blood cultures and cultures of the stool, which were considered necessary because of the positive reactions to the Widal test, yielded no organisms. Later agglutination studies displayed a rising titer for P. vulgaris OX_{19}, which by December 6 was positive in a dilution of 1:5,120. The agglutination titer for typhoid dropped to a level of 1:160. The reaction to the complement fixation test was positive for Rocky Mountain spotted fever and disorders of rickettsial origin in a dilution of 1:64 each.

Results of a biopsy of the skin taken on November 25 were reported as consistent with an arterial lesion of rickettsial origin.

The temperature was normal on the fifth day of therapy, which was the fourteenth day of illness. It rose and remained at 100 to 101 F., with a rise to 102 F. on December 6 and 7, and then a drop to normal on December 8. This course of fever was believed due to formation of an abscess about the site of cannulation in the vein of the left ankle.

Repeated routine urinalyses of voided specimens showed rather consistent reduction of the Benedict solution and albuminuria, even on days that the patient was not receiving dextrose intravenously. Repeated leukocyte counts showed a tendency toward

leukopenia, with a rise in lymphocytes as the child convalesced. The lowest leukocyte count was 5,200 per cubic millimeter.

The child was discharged on December 11, clinically well.

COMMENT

Six cases of children have been presented in which the diagnosis of Rocky Mountain spotted fever was justified on the basis of histories, clinical pictures and available laboratory findings. Neither guinea pig nor egg yolk inoculations were obtainable. However, agglutination for

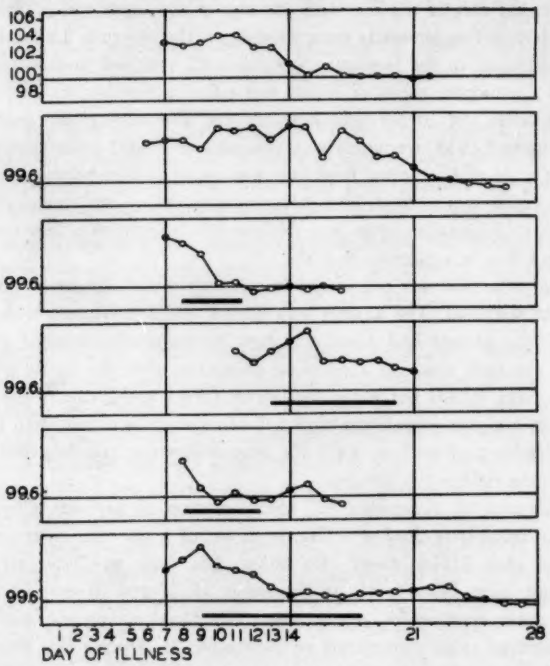

Chart showing variations in body temperatures for cases 1 to 6, in order, from above downward. The heavy black line indicates length of time para-aminobenzoic acid was administered.

P. vulgaris OX_{19}, progressively increasing in titer, and complement fixation tests showing a positive reaction for Rocky Mountain spotted fever established the diagnosis. A history of the presence of ticks in the vicinity, of the typical rash and of a diurnal remittent fever existed in most of the cases. In 4 of the 6 cases biopsies of the skin showed lesions consistent with pathologic changes in the arteries characteristic of rickettsial diseases.

With 1 exception, the temperature of the children treated with para-aminobenzoic acid showed a much more rapid return to normal than would have been expected from comparison with the usual clinical course of Rocky Mountain spotted fever as reported in the literature[10] and exemplified by the 2 children who did not receive the drug. Besides, the treated children became asymptomatic in a much shorter time.

10. Dyer, R. E.: The Rickettsial Diseases, J.A.M.A. **124**:1165-1172 (April 22) 1944.

In the 2 "untreated" children, the fever continued after hospitalization for eleven days and seventeen days, respectively, or for a total of eighteen and twenty-three days of illness. The third child, W. E., was free from fever on the fourth day in the hospital, the eleventh day of illness. B. H., the fifth child, had a normal temperature on the third day of treatment, or the eleventh day of illness, with a slight secondary rise on the seventh and eighth days in the hospital. The last child, T. B., after the eighth day in the hospital, the fifteenth day of illness, showed only a minimal elevation in temperature, which was considered due to an abscess. There was, however, a secondary elevation in temperature on the fifteenth, sixteenth and seventeenth days in the hospital. Administration of para-aminobenzoic acid had been discontinued on the twelfth day in the hospital.

In most of these children, the rash disappeared earlier than in "untreated" children. The general appearance, appetite and mental status improved and edema cleared rapidly. The stay in the hospital was decidedly shortened for W. E. (case 3) and B. H. (case 5) to eleven and ten days, respectively, while C. H. (case 1) and B. K. (case 2) remained in the hospital for sixteen and twenty-one days. The fourth child died on the eleventh day in the hospital, and the last child in the series was hospitalized for several days after he was completely asymptomatic because of an abscess at the site of a venesection.

One death occurred, despite the use of para-aminobenzoic acid. This patient was admitted on the eleventh day of illness after having been treated with a sulfonamide compound for two days. She was delirious, stuporous and bordering on a moribund state at the time of admission. Because of a confusing picture during the first two days in the hospital, the diagnosis was not considered definite enough to begin para-aminobenzoic acid therapy. Slight general improvement was noted during the first twenty-four hours of therapy. At this time she received an intramuscular injection of human immune globulin U.S.P. which was followed by an extreme rise in temperature and a state of shock. It is thought that the amount of human immune globulin used, 10 cc., was excessive and was, therefore, responsible for the high rise in temperature and, possibly, for the state of shock. From this point she became progressively worse, despite intensive supportive therapy. The acidosis which developed was apparently accentuated by an excessive blood level of para-aminobenzoic acid. The patient died on the eleventh day in the hospital.

In an original communication, it was recommended that para-aminobenzoic acid be given in chilled 5 per cent solution of sodium bicarbonate, since it was the authors' opinion that this partial alkalinization would decrease the incidence of gastric irritation and vomiting. The first 3 children received the drug in this manner. Except for oc-

casional vomiting and rare complaints of a burning sensation in the epigastrium, the drug was well tolerated. However, in this age group great difficulty was experienced in getting the patients to take the mixture. Because of this difficulty, the last patient was given the drug in 1 ounce (30 cc.) of orange, grapefruit or tomato juice, and the usual coaxing was not required. Gastritis and vomiting occurred no more frequently than when the drug was given in the solution of sodium

Data on 6 Children With Rocky Mountain Spotted Fever, 4 of Whom Were Treated With Para-Aminobenzoic Acid

Case No.	Age, Yr.	Sex	Day of Illness on Which Therapy Was Started	Duration of Therapy, Days	Duration of Fever After Institution of Therapy, Days	Total Dose, Gm.	Highest Blood Level of Para-Aminobenzoic Acid, Mg./100 Lc.	Complications	Titers of Agglutination Series of Complement Fixation Tests
1	7	M	.....	.....	.....	.....	.....	.....	P. vulgaris OX^{19}: 1:640 Complement fixation: 1:160
2	10	M	.....	.....	.....	.....	.....	.....	P. vulgaris OX^{19}: 1:2,560 Complement fixation: 1:640
3	6	M	9th	4¼	2	78	.....		P. vulgaris OX^{19}: 1:640
4	7	F	13th	7	8	144	262	Vomiting	P. vulgaris OX^{19}: 1:640
5	9	M	8th	5	2	67	34.4	Acidosis; delirium Reducing substance in urine	P. vulgaris OX^{19}: 1:640
6	7	M	9th	10	5	176	82.4	Mild delirium; reducing substance in urine	P. vulgaris OX^{19}: 1:5,120 Complement fixation 1:64

bicarbonate. However, it may be that the elimination of this amount of alkali has been a factor in the production of acidosis in some of the more recently treated children.[11]

Para-aminobenzoic acid was administered in amounts designed to provide blood levels ranging from 30 to 60 mg. per hundred cubic centimeters.[12] Doses were based on recommendations in previous publications.[13] All patients received 4 Gm. as an immediate dose. After this dose, the third patient received 3 Gm. every four hours for four and one-half days. He received a total dose of 78 Gm. No blood level was determined. The fourth child received 3 Gm. at four hour intervals, except for two days when the drug was given every two hours, for a total of seven days of treatment; 144 Gm. in all was given. The blood level, apparently owing to restricted output, reached 262 mg. per hundred cubic centimeters. The fifth child was given 2 Gm. every two

11. Rosenblum, H., and Fraser, L. E.: Effect of Para-Aminobenzoic Acid on Fever and Joint Pains of Acute Rheumatic Fever, Proc. Soc. Exper. Biol. & Med. **65**:178-180, 1947.

12. Method of Marshall and Litchfield, in Methods for Laboratory Technicians, United States War Department, Technical Manual 8-227, Washington, D. C., Government Printing Office, Oct. 17. 1941, p. 134.

13. Flinn and others.[4] Yeomans and others.[7] Smith.[8] Tierney.[9]

hours for the first two days, and then the dose was decreased to 1 Gm. every two hours. The drug was continued for five days, with a total of 67 Gm. given. The highest level obtained was 34.4 mg. The last child was treated for ten days. During this period he received a total of 176 Gm., 2 Gm. of the drug being given every two hours at first, and later 1.5 Gm. at the same time interval. The blood level reached a height of 82.4 mg.

We feel that the number of treated patients in this series is too small to offer any conclusive evidence regarding adequate or optimum dose. However, we are inclined to believe that higher blood levels, if acidosis is prevented, are significantly more beneficial. T. B. (case 6), who was considered practically moribund on admission, improved rapidly as soon as a high blood level was obtained. It is certainly true that, owing to the rapid excretion of the drug, it is impossible to hold an adequate blood level unless the drug is given at frequent intervals. Our experiences led us to believe that it must be given as often as every two or three hours. Flinn and associates[4] suggested that more sustained levels may be obtained when the sodium salt in tablet form is used.

It has frequently been stated that treatment of rickettsial diseases with para-aminobenzoic acid must be started early in the disease in order to obtain maximum effect.[7] Treatment with the drug of the 3 children who reacted favorably was started on the eighth or the ninth day of the illness. The child who died did not receive therapy until the thirteenth day of illness, and we feel that this delay was, in part, responsible for the unfavorable outcome. It seems particularly true that early therapy is necessary in the severer cases.

No serious complications were mentioned in previous communications on this subject, except the development of leukopenia,[14] which disappeared when the drug was discontinued, and of some degree of mental confusion and delirium.[15] In 2 of our patients a relative leukopenia developed. B. H. (case 5) showed a drop in leukocyte count from 8,500 to 5,050 between the third and fifth days of therapy. This lower level was obtained at the end of the course of treatment, and no further decrease was noted. T. B. (case 6) also had a drop in leukocyte count to 5,200, but no evidence of agranulocytosis developed.

The child in whom the excessive level of 262 mg. was obtained became definitely acidotic, with acetone in the urine and a carbon dioxide-combining power of 18 volumes per cent. More pronounced delirium was also noted. It seems certain that acidosis can develop with much lower levels than this, unless an adequate amount of base is given.[11] We believe that delirium and confusion reportedly produced by

14. Yeomans and others.[7] Smith.[8] Tierney.[9]

15. Yeomans and others.[7] Tierney.[9]

para-aminobenzoic acid in the past may be due to varying degrees of acidosis rather than to the drug itself. Also, acidosis occurring as a result of the disease may add insult. Treatment of the acidosis in the child just mentioned with sixth-molar solution of sodium lactate lessened the delirium and mental confusion. It may be true that if an adequate amount of a base is given to prevent the development of an alkali deficit with resultant acidosis, a much higher blood level of para-aminobenzoic acid may be obtained without development of these symptoms.

An incidental observation on 2 of the children was the presence of a reducing substance in the urine during the therapy. We are unable to explain the cause or significance of this finding, but we have detected its presence repeatedly in several children who were in another series treated with the drug. Investigations to determine the cause for and type of the reducing substance present in the urine during the administration of para-aminobenzoic acid are being made.

SUMMARY AND CONCLUSIONS

Reports of 6 cases of Rocky Mountain spotted fever in children are presented. In 4 of these cases para-aminobenzoic acid was used, and the other 2 are presented for their comparative value.

Three of the treated children, for whom therapy was begun on the eighth or ninth day of illness, responded rapidly. The drug was considered of definite value for these children.

A child for whom therapy was instituted on the thirteenth day died.

We do not agree with previous reports that para-aminobenzoic acid is a drug of low toxicity, since in 1 of these children extreme acidosis developed. It is true that the blood level of the drug was extremely high. Administration of an adequate amount of base in some form is recommended, with careful following of the blood levels, urinary findings and carbon dioxide-combining power.

The complications of delirium and mental confusion probably are due to varying degrees of acidosis rather than to the drug per se, although the disease itself may produce delirium and acidosis.

An incidental observation of a reducing substance in the urine is reported.

NOTE.—Since we wrote this article, several pharmaceutic companies have begun manufacturing the sodium salt of para-aminobenzoic acid. This compound was used in later cases, and the appearance of acidosis was not noted. A convenient dosage plan was outlined by Ravenel,[16] who recommended administration of 0.5 to 1 Gm. per pound of body weight per day in divided doses, depending on the size of the child, larger patients receiving the smaller and smaller patients the larger dose.

16. Ravenel, S. F.: The Treatment of Rocky Mountain Spotted Fever with Para-Aminobenzoic Acid: A Comprehensive Plan, South. M. J. **40**:801-813, 1947.

DETECTION OF MILD TYPES OF MEDITERRANEAN (COOLEY'S) ANEMIA

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IN 1925 and in 1927, Cooley and his associates[1] drew attention to an anemia which had heretofore been regarded as belonging to the heterogeneous group of von Jaksch's anemia, but which possessed such well defined features as to constitute a clinical entity. The outstanding characteristics of this condition are the familial and racial tendencies, the progressive anemia, marked distortion of the red cells, large numbers of normoblasts, the occurrence of jaundice, splenomegaly and, frequently, hepatomegaly, the mongoloid facies and definite roentgenographic changes. The patients are mainly of Greek, Italian (principally Sicilian) or Syrian ancestry. Since Cooley's original description, an increasing number of cases of the severe form of the disease has been frequently reported. The prognosis for the severe form of the disease with symptoms dating from the first two years of life is unfavorable, although with frequent transfusions children have been carried beyond adolescence.

In familial studies of patients with the severe form of the disease, it has been observed that the siblings and parents may possess the clinical and hematologic features of Mediterranean anemia (familial erythroblastic anemia) ranging in severity from the trait for the disease to a moderate anemia. The identification of these affected persons and the hereditary transmission of the disease have been the subjects of several investigations in recent years.[2]

From the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

Presented at the combined meeting of the Section of Pediatrics of the New York Academy of Medicine and the Society for the Study of Blood, Nov. 14, 1946.

1. *(a)* Cooley, T. B., and Lee, P.: Series of Cases of Splenomegaly in Children with Anemia and Peculiar Bone Changes, Tr. Am. Pediat. Soc. **37**:29-30, 1925. *(b)* Cooley, T. B.; Witwer, E. R., and Lee, P.: Anemia in Children with Splenomegaly and Peculiar Changes in the Bones: Report of Cases, Am. J. Dis. Child. **34**:347-363 (Sept.) 1927.

(Footnotes continued on next page)

IMPORTANCE OF DETECTING THE CARRIER

While well established cases of Mediterranean anemia are readily diagnosed, the milder form is usually overlooked. The present report is prompted by the increasing frequency with which this milder type has been encountered in the Children's Clinic of the New York Hospital and by the probability that it is also prevalent in other communities with large Mediterranean populations. The reason for recognizing healthy persons who are carriers and who possess the trait for this disease is that they constitute a potential source for the hereditary transmission of the disease in any of its clinical forms, from the mildest to the severest. There is increasing evidence, for instance, that the severe form of the disease, which requires frequent transfusions and which may be fatal, is likely to occur when both parents possess the trait for the disease. Furthermore, the diagnosis of Mediterranean anemia in a child with an obscure anemia of moderate severity can often be made earlier in its course, and useless therapy avoided, by the detection of the trait in the parents and siblings.

SUSCEPTIBLE POPULATION IN THE UNITED STATES

If the frequency with which the mild type of Mediterranean anemia is encountered in New York city represents an indication of its extent among persons of Mediterranean origin in other parts of the United States, this condition must be extremely prevalent. Neel and Valentine,[3] on the basis of the known incidence of the severe form,

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2. *(a)* Caminopetros, J.: Recherches sur l'anemie erythroblastique infantile des peuples de la Mediterranee orientale. Etude anthropologique, etiologique et pathogenique; la transmission hereditaire de la maladie, Ann. de med. **43**:27-61 (Jan.); 104-125 (Feb.) 1938. *(b)* Atkinson, D. W.: Erythroblastic Anemia: Report of Two Cases in Adult Siblings with Review of Theories as to Its Transmission. Am. J. M. Sc. **198**:376-383 (Sept.) 1939. *(c)* Wintrobe, M. M.; Matthews, S.; Pollack, R., and Dobys, B. M.: A Familial Hemopoietic Disorder in Italian Adolescents and Adults Resembling Mediterranean Disease (Thalassemia), J.A.M.A. **114**:1530-1538 (April 20) 1940. *(d)* Strauss, M. B.; Daland, G. A., and Fox, H. J.: Familial Microcytic Anemia: Observations on Six Cases of Blood Disorders in an Italian Family, Am. J. M. Sc. **201**:30-34 (Jan.) 1941. *(e)* Pierce, M. I.: Erythroblastic Anemia: A Clinical Study, Am. J. Dis. Child. **61**:654 (March) 1941. Cooley, Witwer and Lee.[1b] *(f)* Smith, C. H.: Mediterranean (Cooley's Anemia in a Youth of Nineteen Years Observed Since Early Childhood: Familial Aspects and Hematologic Features of "Carrier" or Asymptomatic Case, J. Pediat. **20**: 370-382 (March) 1942. *(g)* Goldhamer, M. L.: Mediterranean Anemia in the Adult (A Family History Analysis), Ohio State M. J. **38**:321-324 (April) 1942. *(h)* Dameshek, W.: Familial Mediterranean Target-Oval Cell Syndromes, Am. J. M. Sc. **205**:643-660 (May) 1943. *(i)* Smith, C. H.: Familial Blood Studies in Cases of Mediterranean (Cooley's) Anemia, Am. J. Dis. Child. **65**:681-701 (May) 1943. *(j)* Valentine, W. N., and Neel, J. V.: Hematologic and Genetic Study of the Transmission of Thalassemia (Cooley's Anemia; Mediterranean Anemia), Arch. Int. Med. **74**:185-196 (Sept.) 1944.

3. Neel, J. V., and Valentine, W. N.: The Frequency of Thalassemia, Am. J. M. Sc. **209**:568-572 (May) 1945.

recently computed that the mild form occurred in approximately 1 out of 25 adult Italians in the city of Rochester, N. Y. In the sixteenth census of the United States[4] the number of Italians, Greeks and

TABLE 1.—*Nativity and Parentage of Foreign White Stock of Mediterranean Origin**

	Foreign-Born White Persons	Native White Persons of Foreign or Mixed Parentage	Total
Italy	1,623,580	2,971,200	4,594,780
Greece	163,252	163,420	326,672
Syria	50,859	87,740	138,599
Total	1,837,691	3,222,360	5,060,051

*Data are from the sixteenth census of the United States, 1940. These figures comprise those persons who were born abroad or who had at least one foreign-born parent. Exact statistics of the generation of children susceptible to Mediterranean anemia with native-born parents and grandparents who are of Mediterranean origin are not available.

Fig. 1.—Distribution of foreign white stock of Mediterranean origin in the United States (from the sixteenth census of the United States: 1940). Each dot represents 25,000 to 50,000 persons of Mediterranean extraction. Although every state is represented by varying numbers of such persons, California, Connecticut, Illinois, Massachusetts, Michigan, New Jersey, New York, Ohio, Pennsylvania and Rhode Island account for a majority of the total.

4. Population: Nativity and Parentage of the White Population, Country of Origin of the Foreign Stock, in Sixteenth Census of the United States, 1940, United States Department of Commerce, Bureau of the Census, 1943.

Syrians, designated as "foreign white stock" consisting of foreign-born white and native white persons of foreign and mixed parentage, reached a total of more than 5,000,000 persons (table 1). In New York city alone, there are approximately 53,250 persons of Greek origin and 1,095,000 persons of Italian origin. Not included in the census figures is the large number of susceptible children whose parents were both born in the United States, but one or more of whose grandparents were born in the Mediterranean countries. The bulk of Italians represented in these statistics immigrated to the United States from the southern part of their country in the latter half of the nineteenth century and in the beginning of the twentieth,[5] and it is in this group that the largest number of cases of Mediterranean anemia occur. The nativity and parentage of the foreign white stock of Mediterranean origin and the areas of the largest concentrations of these persons in the United States are presented in table 1 and in figure 1, respectively.

DIAGNOSTIC CRITERIA OF THE MILD TYPE OF MEDITERRANEAN ANEMIA

The conspicuous roentgenographic changes and pronounced clinical manifestations that characterize the severe form of Mediterranean, or Cooley's, anemia are absent in the person with the mild form of the disease. Diagnosis of the mild type depends on the evaluation of data derived from a variety of sources:

1. Patients are usually of Mediterranean origin, principally Greek and Italian.
2. Patients are asymptomatic, mildly anemic or without anemia.
3. Blood smear and blood count show hypochromic macrocytes, basophilic stippling, oval and target cells, polycythemia.
4. Morphologic changes in erythrocytes are far in excess of the degree of anemia.
5. Resistance of the red cells to hemolysis in hypotonic solutions of sodium chloride is increased.
6. Iron or other forms of antianemia therapy fail to restore normal blood levels.
7. The trait may be detected in parents and in siblings.

INVESTIGATION OF THE COUNTRY OF ORIGIN

Precise information concerning race and nationality of the parents and grandparents of the patient contributes to the diagnosis of the mild type of Mediterranean anemia. Lately, a few authentic cases of this disease have been recognized among persons of Chinese,[6] Asiatic Indian,[7]

5. Foerster, R. F.: The Italian Emigration of Our Times, Cambridge, Mass., Harvard University Press, 1919, chap. 17.

6. Foster, L. P.: Cooley's Syndrome (Erythroblastic Anemia) in a Chinese Child, Am. J. Dis. Child. **59**:828-834 (April) 1940.

7. Dhayagude, R. G.: Erythroblastic Anemia of Cooley (Familial Erythroblastic Anemia) in an Indian Boy, Am. J. Dis. Child. **67**:290-293 (April) 1944.

Turkish,[8] Spanish,[9] and Egyptian origin,[10] among the natives of Cyprus[11] and in one instance in a Negro girl.[12] Two cases have been described[13] in Bucharan Jews, those of a girl, 14 years of age and of her brother, aged 30, whose ancestors lived on the shores of the Caspian Sea. Notwithstanding these reports, the majority of cases in this country have been restricted to children of Italian, Greek or Syrian ancestry. In the present series of patients, except for 2 families originating in Turkey, the parents or grandparents were born in the cities of southern Italy included in the provinces Campania, Lucania, Calabria and Apulia, in Sicily and in Greece. In 20 families both parents of an affected child were born in the United States, but in every instance one or more grandparents were of Greek or Italian extraction. The birth of a parent in Italy or in Greece, therefore, need no longer be regarded as a requirement for the diagnosis of Mediterranean anemia, provided the ancestry is followed to the grandparents. Recently, a number of cases of the established disease have been observed among the Chinese in New York city, so that a search for the milder forms in this racial group is also warranted.

CLINICAL FEATURES

In persons with the trait and with the mild form of the disease, the changes in the bones were usually absent or equivocal. Occasionally, a mild osteoporosis may be noted, but the characteristic skeletal changes produced by the extreme marrow hyperplasia, which are reflected in the roentgenograms in the patient with the advanced form of the anemia, are absent. Persons with the trait and with the mild type do not show the cardiac murmurs, enlargement of the heart or bone and pain in the joints noted in the severe form. Persons with the milder types of Mediterranean anemia are of normal appearance and bear no facial resemblance to those with the established form of this disease. They are asymptomatic, and the condition would have escaped detection without careful examination of the blood. In children with the mild disease,

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8. Saracoglu, K.: Cooleysche Anaemie in der Tuerkei, Wien. med. Wchnschr. **93**:217 (March 20) 1943.

9. Jaso, E.; Ales Reinlein, J. M., and Pardo Urdapilleta, J.: El primer caso espanol de anemia de Cooley, Rev. clin. espan. **4**:425-429 (March 30) 1942.

10. Diwani, M.: Erythroblastic Anaemia with Bone Changes in Egyptian Children, Arch. Dis. Childhood **19**:163-168 (Dec.) 1944.

11. Fawdry, A. L.: Erythroblastic Anaemia of Childhood (Cooley's Anaemia) in Cyprus, Lancet **1**:171-176 (Feb. 5) 1944.

12. Faber, H. K., and Roth, B. M.: Mediterranean Anemia (Cooley) in a Negro Girl, J. Pediat. **28**:610-612 (May) 1946.

13. Schieber, C.: Target Cell Anemia; Two Cases in Bucharan Jews, Lancet **2**:851-852 (Dec. 29) 1945.

either pallor or a palpable spleen, or both, led to the examination of the blood. The significance of the mild anemia which resisted iron therapy and the slight enlargement of the spleen might have been overlooked had not attention been attracted to the Mediterranean origin of the children.

EXAMINATION OF THE BLOOD

This presentation is based on the changes in the blood in 47 families with Mediterranean anemia, 16 of which had been previously reported on.[21] The detailed clinical and hematologic data for members of the additional group of families will be reported in a later communication. In 35 of the families both parents were available for study, and in 12 examination was confined to a single parent. Including 3 adults who were related to the families under consideration, the blood of 181 persons was analyzed, of whom 27, all children, were severely anemic and 131, including parents and siblings, had the trait for or the mild type of this disease. Among the persons with the mild type were included 42 persons of the earlier group, many of whom had since that time had repeated examinations of the blood. With this added experience, it is now possible to set forth the criteria for diagnosis of the milder form with greater accuracy and certainty.

In the present study only those hematologic procedures were carried out which were essential in screening out all forms of this disease. During the course of this study it became apparent that the technical problems involved in the diagnosis of the milder type of Mediterranean anemia were of such magnitude that only essential and simplified procedures could be employed. It was also felt that similar studies might be carried out in other parts of the country so that experience with the series of cases in this hospital might be of value in other areas with susceptible populations.

Methods of Study.—The determination of the hemoglobin content, the red cell count, the measurement of the volume of packed red cells with the hematocrit, the fragility test and the examination of the blood smear constitute the essential laboratory procedures in the diagnosis of Mediterranean anemia.

Volume of Packed Red Cells.—The present series confirmed the observation made previously that the measurement of the volume of packed red cells with the hematocrit constitutes the most accurate single laboratory procedure for diagnosis and therapy in Mediterranean anemia. Since the determination reflects the total mass of red cells in a unit volume of blood, it has proved of fundamental value in this anemia, in which considerable alterations occur in the size, shape and thickness of the red cells. It has been repeatedly shown that the red cell count may be misleading in this disease because of the striking thinness of

the erythrocytes and also because of the alterations in their size, so that the total count may approach normal levels, despite a considerable reduction in the hematocrit value. In the asymptomatic person with the milder form of Mediterranean anemia, the volume of packed red cells frequently remains at the same level in spite of wide fluctuations in the number of red cells.

For measuring the volume of packed red cells with the use of blood from the finger, the method previously described[14] has continued to prove reliable and particularly useful for infants and children for whom repeated venipuncture is undesirable. This method, which was especially designed for small blood samples, has proved superior to other micromethods. It requires a minimum of technical skill and calculation, and the values with this method coincide exactly with those obtained with venous blood. This measurement has proved to be essential in the management of all forms of Mediterranean anemia, especially the severe type. In the outpatient transfusion clinic at the New York Hospital,[15] experience has shown that the measurements of the hemoglobin content and the hematocrit readings constitute indispensable guides in gaging the frequency of transfusions and amounts of blood to be administered.

A small sample of blood from the finger[16] obtained by deep puncture is collected directly into a test tube, *A* (fig. 2) containing dried anticoagulant. With vigorous shaking, the blood is quickly forced to the bottom of the tube and thoroughly mixed. It is transferred from the tube, *A*, to the hematocrit, *C*, by means of a capillary pipette, *B*, and centrifuged for half an hour at 2,500 revolutions. The number of millimeters of packed cells multiplied by 2 constitutes the hematocrit reading in percentage. A hematocrit reading of 36 per cent represents

14. Smith, C. H.: A Method for Determining the Sedimentation Rate and Red Cell Volume in Infants and Children with the Use of Capillary Blood, Am. J. M. Sc. **192:** 73-86 (July) 1936.

15. Koteen, P., and Brooks, N.: Establishment of a Transfusion Clinic, J. Pediat. **28:**697-702 (June) 1946. Koteen, P., and Smith, C. H.: Transfusion Clinic for Out-Patients, Mod. Hosp. **66:**57-58 (June) 1946.

16. Approximately 0.3 to 0.4 cc. of blood is required for determination of hemoglobin content and hematocrit reading. This amount of blood is estimated and does not have to be measured exactly. Tubes for collecting blood should measure 1 cm. in width and 4 cm. in length. In a tube with these specifications, the blood collected should occupy a space of 1 cm. from the bottom. The anticoagulants are either heparin or mixed oxalates and may be prepared as follows: Three drops of a solution of heparin, prepared by dissolving 50 mg. in 4 cc. of distilled water, or of an oxalate mixture (1.5 Gm. of ammonium oxalate and 1 Gm. of potassium oxalate dissolved in 100 cc. of water as recommended by Heller and Paul (Heller, V. G., and Paul, H.: Changes in Cell Volume Produced by Varying Concentrations of Different Anticoagulants, *J. Lab. & Clin. Med.* **19:**777-780 [April] 1934.), are slowly evaporated to dryness in a test tube. The hematocrit required for the test may be obtained from E. Machlett & Son, 220 East Twenty-Third Street, New York.

the average normal level for infants and children, and one of 40 per cent, the normal level for persons in older age groups. In the treatment of the severe form in a hospital where there are no facilities for periodic transfusions in the outpatient department, no child of any age should be discharged without a hematocrit reading of 40 per cent of packed red cells.

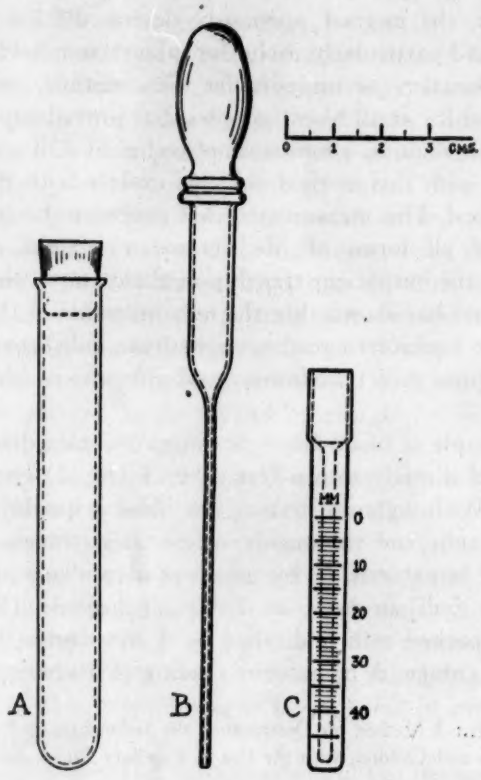

Fig. 2.—Hematocrit for measuring volume of packed red cells using blood from the finger. Blood is collected in test tube *A* containing dried anticoagulant material and is transferred by means of the pipet *B* to the hematocrit *C*.

Fragility Test.—The increased resistance of the red corpuscles, as noted in fragility tests, constitutes one of the more important criteria in the diagnosis of all types of Mediterranean anemia. Prolongation of the fragility span indicates that the bulk of red cells in this disease possess relatively large cell surfaces in contrast with their substance. Careful comparison with a control and, in doubtful cases, microscopic examination of the unhemolyzed cells from the tubes with the more dilute solutions of sodium chloride are occasionally needed.

When large numbers of tests are required, however, several technical difficulties are encountered which preclude frequent performances of the fragility test, especially when family surveys are necessary. The problems involved include preparation of an adequate number of tubes containing serial dilutions of hypotonic solution of sodium chloride, the use of venous blood in small children and the need for a control in each period.

While it is known that the span of fragility is greatly increased in Mediterranean anemia and that intact red blood cells may be seen in the lowest dilutions of sodium chloride solution, experience has shown that the tubes containing certain of the concentrations offer information of a decisive diagnostic character. In numerous fragility tests, it was noted that the blood of the person with Mediterranean anemia of any grade of severity showed a much heavier sediment of intact red cells and a supernatant fluid that was less hemolyzed in the tubes containing 0.375, 0.35 and 0.325 per cent of sodium chloride than was seen in the corresponding tubes of the control.

A screening test was therefore devised utilizing blood from the finger in these three concentrations of hypotonic solution of sodium chloride. The technical details of this test have been described in another communication.[17] The result of a series of comparative tests employing venous blood revealed the complete reliability of the shorter procedure.

This method is not meant to replace the more comprehensive fragility test utilizing venous blood, but it was devised solely as a gross method of screening out large numbers of patients suspected of having Mediterranean anemia. With the use of blood from the finger, controls are readily available, and in normal persons the degree of hemolysis in the three tubes is as follows: with 0.375 per cent sodium chloride, 3 plus; with 0.35 per cent, 3 or 4 plus, and with 0.325 per cent, 4 plus. The simplicity of comparing the degree of hemolysis in the blood of the suspected patient with that of a normal control utilizing blood from the finger in the three diagnostic concentrations is apparent.

Blood Smear and Blood Count.—The occurrence of morphologic changes far in excess of the degree of the anemia pointed out by Wintrobe and associates[2c] constitutes a fundamental principle in the detection of the mild form of the disease. A sharp distinction cannot always be made between the person with the trait and one with the mild type, since the difference is one of degree. The former condition manifests no anemia, while the latter reveals a slight reduction in hemoglobin content and in the volume of packed red cells, but in both the blood shows an

17. Smith, C. H.: The Diagnosis of Anemias in Infancy and Childhood, J.A.M.A. **134**:992-997 (July 19) 1947.

increased resistance to hypotonic solution of sodium chloride, as well as other significant hematologic abnormalities in the red corpuscles. The mild anemia is qualitatively similar to, but less in degree than, that which occurs in the severe form of Mediterranean anemia. Patients with the mild form of the disease have also been designated as carriers, a term employed in a limited genetic sense to describe the asymptomatic person with minimal changes in the blood. The ability to detect a carrier of this disease corresponds to that of recognizing similar persons with the trait for congenital hemolytic anemia or for sickle cell anemia. With the tests employed, the commonest findings, regardless of the anemia, are hypochromic macrocytes, stippled red cells, increased resistance of the red cells to hemolysis in hypotonic solutions of sodium chloride and, less frequently, polycythemia and target and oval cells.

In enumeration of the changes in the blood cells, it should be emphasized that except for the abnormal thinness of the red cell, which has still to be more thoroughly evaluated, there are no diagnostic cells in Mediterranean anemia. Target cells, oval cells, hypochromic macrocytes and stippled red cells appear in certain stages of many anemias and therefore cannot be regarded as specific hematologic features of a single disease. They are of diagnostic value only when considered in conjunction with pertinent information obtained from other sources.

It has been my experience that there are mild cases in which the results of the fragility test are equivocal, abnormalities in the blood smear being present but frequently overlooked. In these cases, variations in the preparation of the blood film and in staining technic will reveal red cells with basophilic stippling, hypochromic macrocytes and the other diagnostic cytologic features of the trait. The necessity for a careful examination of the blood smear applies particularly in case of those parents who have one child with severe anemia and who contemplate future pregnancies. With training, an investigator can detect the mild forms of the disease, and it is unwise to regard the members of the family of an affected patient as entirely normal hematologically until many slides have been thoroughly scrutinized.

Hypochromic Macrocytes.—The great variation in the mean volume of red cells which serves as an index of their size is apparent in table 2. Since the mean volume of red cells represents the ratio between the volume of the packed cells and the erythrocyte count, the smaller size of the cell in the mild form usually results from an increased number of red cells in relation to the normal or slightly lowered volume of the packed cells. While the mean size of the cells connotes a tendency to microcytosis, the blood film does not reveal a uniform picture of microcytes as in anemia resulting from iron deficiency. The stained blood films usually show an admixture of hypochromic microcytes and cells with varying degrees of poikilocytosis and anisocytosis, but the distinguishing feature is the interspersion of erythrocytes of larger size.

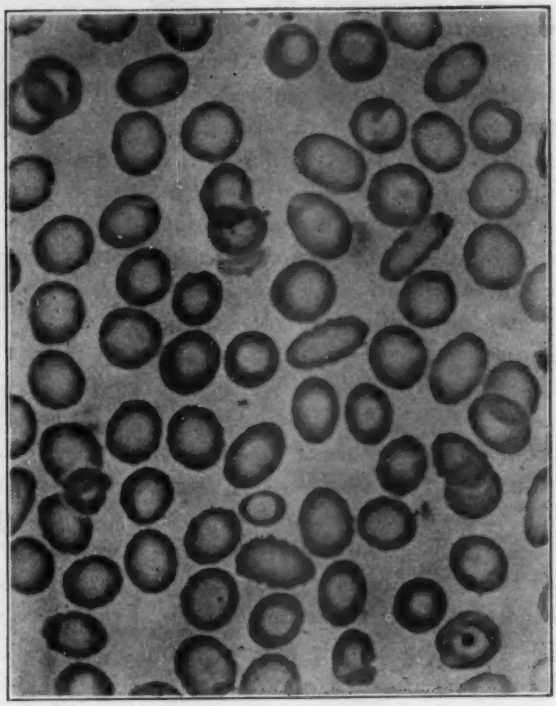

Fig. 3.—Photomicrograph (× 900) of a blood smear of A. A., father of J. A. (fig. 6). Note anisocytosis, poikilocytosis, oval cells and predominance of hypochromic macrocytes. The macrocytic appearance of the blood film constitutes a characteristic feature of many of the mild forms of Mediterranean anemia.

TABLE 2.—*Gradations of Severity in Mediterranean Anemia**

Subject	Age, Yr.	Hemoglobin, Gm.	Red Cells, Millions	Hematocrit, %	Mean† Red Cell Volume, Cubic Microns	Mean‡ Hemoglobin Concentration, %	Macrocytes	Stippling	Fragility Test§ Hemolysis % Solution Na Cl Begins	Ends
Examples of the trait										
A.T.	12	12.2	6.5	40	62	31	+++	++	0.375	0.2
D.R.	29	14.6	6.35	43	68	34	++	+	0.375	0.25
C.C.	48	14.0	5.6	43	77	33	++	++++	0.4	0.25
Examples of mild cases										
DiN.	2	10.0	5.1	32	63	31	+++	+	0.375	0.25
V.DiG.	3½	10.5	4.8	34	71	31	++	++++	0.35	0.2
S.S.	36	11.0	5.8	34	59	32	++	++	0.4	0.225
Examples of moderate cases										
D.M.	18¾	8.0	3.75	34	90	24	+++	+	0.4	0.25
S.M.	7¾	9.0	3.36	30	89	30	+++	+	0.425	0.225
A.G.	18	8.2	2.70	26	96	32	+++	+	0.425	0.15
L.G.	13	7.8	2.47	24	97	33	++++	+	0.425	0.15
Examples of severe cases										
J.A.	1	4.8	2.10	15	71	32	+++	+	0.4	0.15
I.C.	7	6.5	2.7	22	81	30	++++	++	0.4	0.15

*Note that qualitatively similar alterations in the blood occur in all forms of the disease, from the mildest without anemia to the severe types requiring transfusions.

†Mean red blood cell volume, cubic microns =
Volume of packed red cells (hematocrit), cc. per 1000 cc.
Red cell count, millions per c. mm.
Normal values = 80 to 90 cubic microns.

‡Mean hemoglobin concentration in red cells—cells (mean corpuscular hemoglobin concentration) = Hemoglobin, Gm. per 100 cc. × 100
Volume of packed red cells, cc. per 100 cc.
Normal values = 32 to 38 per cent.

§Normal range approximately 0.425 per cent to 0.325 per cent solution sodium chloride.

These macrocytic cells possessing diminished pigment constitute one of the most important diagnostic features of the blood smears of patients with the trait for and the mild form of the disease and are especially prominent in blood smears characterized by microcytosis. They are usually identified in the thin portion of the blood film where no overlapping of cells occurs. The type of macrocyte most frequently observed in the milder form is round, occasionally somewhat oval, with a contracted margin of hemoglobin and a larger central hypochromic area. Some of these cells are polychromatophilic, and in others the central area reveals a faintly or deeply stained island of hemoglobin producing a target-like appearance.

It will be observed in table 2 that the red cell volume is greater in the moderate or severe types than in the milder forms. The striking appearance of the blood smears of the patients with the severe form of Mediterranean anemia is due to large numbers of excessively thin hypochromic macrocytes of unusual proportions. Although the red cells do not reach the same size or degree of thinness or hypochromia as in the advanced types, this macrocytic aspect of the blood constitutes a valuable diagnostic feature of the milder form of the disease (fig. 3).

Basophilic Stippling.—With few exceptions, the appearance of stippled red cells constituted a noteworthy sign in the blood of most persons in this series. The presence of excessive numbers of erythrocytes with punctate basophilia in persons with normal blood levels is difficult to reconcile with the concept of stippling as an index of regeneration, since there appears to be no need for accelerated hematopoiesis in the absence of anemia. Basophilic stippling may be sufficiently pronounced to suggest lead posioning. Stippling in this disease may reflect not an immaturity of the red cells, as it is usually interpreted, but a corpuscular abnormality which is either degenerative or congenital in nature. More specifically, the defect may be located in the cell envelope, resulting in precipitation of the basophilic substance when stains are applied. Added evidence that the involvement of the cell envelope is the fundamental hereditary anomaly is provided by the observation that 1 or more affected children and a parent in 1 family frequently demonstrated corresponding increases in the number of stippled red cells, as well as punctate basophilic granules of similar size and pattern.

Blood films prepared in the routine manner with Wright's stain readily reveal stippled red cells when they are numerous and when the granules are large. If other features suggestive of Mediterranean anemia are present either in the blood smear or as indicated by a prolonged span of fragility, modifications in the time of staining will usually reveal the granules of the stippled red cells when casual examination shows none. A persistent search for stippling should be made whenever polychromatophilic red cells are observed in the blood smear, since the phenomena are closely related. For this reason, as a routine in the

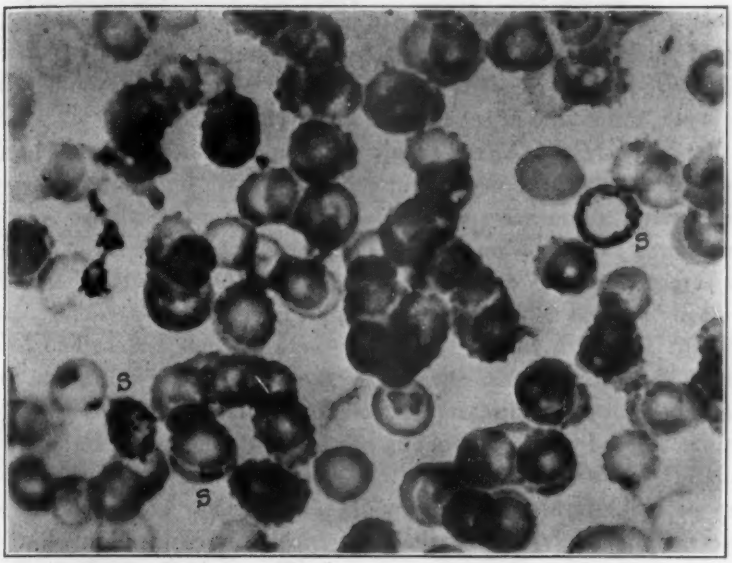

Fig. 4.—Photomicrograph (× 900) of a blood smear of L. A. (fig. 7), a child with the mild type of Mediterranean anemia. Note presence of 3 stippled red cells (indicated by *s*) in one microscopic field.

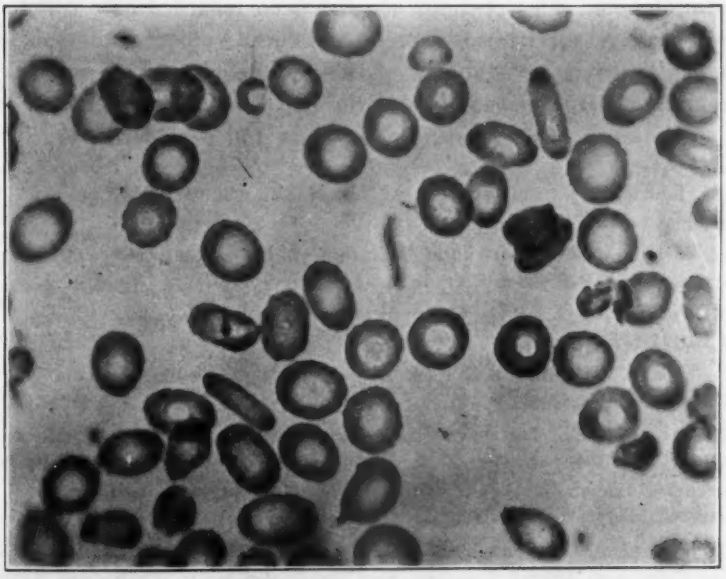

Fig. 5.—Photomicrograph (× 900) of blood smear of R. C., maternal aunt of patient D. B. (fig. 6), demonstrating anisocytosis, poikilocytosis, hypochromic macrocytes, oval, elongated and rodlike cells.

present study at least two blood smears were prepared on slides, one slightly thicker than the other. The thicker smear, when slightly overstained, frequently revealed the presence of punctate basophilia when it was not observable in the thinner smear (fig. 4).

Target and Oval Cells.—Target cells appeared in the blood of fewer than half the patients, while oval cells were more frequently observed. In common with other anemias,[18] many varieties of elliptic cells are encountered ranging from oval to elongated and rodlike forms (fig. 5). The target corpuscle was originally so named by Barrett[19] because of its deeply stained center and periphery which are arranged in concentric light and dark zones. These cells were originally identified in the smears of Mediterranean anemia by Bywaters[20] and Smith[21] as nonspecific signs of this disease. The evidence that the target cell is not peculiar to Mediterranean anemia has been accumulating,[22] and Valentine and Neel[23] recently described the production of these cells in vitro from normal erythrocytes. Although target and oval cells occur in a variety of blood dyscrasias, their presence nevertheless contributes to the diagnosis of Mediterranean anemia. To minimize confusion as to terminology and classification it appears advisable to absorb the term "target cell" anemia[24] into the category of Mediterranean anemia.

Polycythemia.—Elevated red cell counts occur in the milder forms of Mediterranean anemia and may occasionally exceed 6,000,000 per cubic millimeter. This phenomenon has been regarded as a compensatory physiologic mechanism for cells of reduced volume and hemoglobin content. The relative stability of the volume of packed red cells as compared with the inconstancy of the red cell count, which may vary in the same person between normal values and a moderate erythrocy-

18. Florman, A. L., and Wintrobe, M. M.: Human Elliptical Red Corpuscles. Bull. Johns Hopkins Hosp. **63**:209-220 (Oct.) 1938.

19. Barrett, A. M.: Special Form of Erythrocyte Possessing Increased Resistance to Hypotonic Saline, J. Path. & Bact. **46**:603-618 (May) 1938.

20. Bywaters, E. G. L.: The Cooley Syndrome in an English Child, Arch. Dis. Childhood **13**:173-187 (June) 1938.

21. Smith, C. H.: Anemias of Early Infancy: Pathogenesis and Diagnosis, J. Pediat. **16**:375-395 (March) 1940.

22. Bohrod, M. G.: The Significance of Target Cells in Anemia, Am. J. M. Sc. **202**: 869-874 (Dec.) 1941. Cooley, T. B.: Hereditary Factors in the Blood Dyscrasias: President's Address. Am. J. Dis. Child. **62**:1-8 (July) 1941. Greenblatt, I. J., and Kaplan, G.: Target Cells in Postvaccinal Jaundice, J.A.M.A. **122**:806-807 (July 17)

23. Valentine, W. N., and Neel, J. V.: The Artificial Production and Significance of Target Cells, with Special Reference to Their Occurrence in Thalassemia (Cooley's Erythroblastic Anemia), Am. J. M. Sc. **209**:741-752 (June) 1945.

24. Dameshek, W.: "Target Cell" Anemia: Anerythroblastic Type of Cooley's Erythroblastic Anemia, Am. J. M. Sc. **200**:445-454 (Oct.) 1940.

tosis, has been frequently observed in patients who exhibit the milder degrees of Mediterranean anemia. The discrepancy between these two values, which also emphasizes the importance of measuring the volume of packed red cells, is illustrated in table 3. In this case of a boy 10

TABLE 3.—*Variations of the Red Blood Cell Count in Patient N. R.*

Date, 1945	Hemoglobin, Gm.	Red Cells, Million	Hematocrit, %
March 27	11.8	5.0	36
April 17	11.5	5.3	35
May 22	11.8	7.2	35
June 12	10.5	6.0	38
July 24	12.0	5.3	36

years of age, the presence of the mild type was suspected when his anemia proved refractory to iron therapy.

GRADATIONS OF SEVERITY IN MEDITERRANEAN ANEMIA

Cases of Mediterranean anemia demonstrate a continuous range from the mildest form without anemia, but with well defined morphologic changes in the blood smear, to the overt types requiring periodic transfusions (table 2). In observing patients over extended periods, it is noteworthy that, except for those requiring transfusions, the blood levels are distinctive for each person and are maintained within a narrow range.

TABLE 4.—*Blood Studies in Family of F. R., Five Members of Which Had the Mild Type of Mediterranean Anemia**

	Father F.R.	Mother M.R.	Sister J.R.	Patient M.R.	Patient F.R.	Patient V.R.	Patient M.R.
Age, yr.	42	36	16	11	9	4	3
Hemoglobin, Gm.	14	12	13.5	9.8	8.5	9.8	11.2
Red cells, millions	5.9	5.5	4.18	4.2	3.1	5.58	6.01
Hematocrit, per cent	42	40	43	34	32	34	35
Mean red cell volume, cubic microns	71	73	103	81	103	61	58
Hemoglobin concentration in red cells, per cent	33	30	31	29	27	29	32
Stippling	0	+++	0	+	+	+	++
Hypochromic macrocytes	10	++	0	++	+	+++	+++
Target cells	0	0	0	+	+	+	+
Oval cells	0	++	0	++	++	++	++
Fragility Test							
Hemolysis begins	0.4	0.4	0.425	0.375	0.375	0.35	0.4
Hemolysis ends	0.325		0.3	0.275	0.25	0.225	0.25

*The father, F. R., and one daughter, J. R., are unaffected. Note that the mother, M. R., and 4 children, M. R., F. R., V. R., and M. R., reveal hematologic evidences of the mild type of the disease.

The mean corpuscular hemoglobin concentration, which represents the percentage ratio of hemoglobin in grams to the volume of packed red cells in each 100 cc. of blood, is usually not greatly reduced below the minimal normal level of 32 per cent. This apparent inconsistency in patients with anemia results from the thinness of the red cell, so that for its small volume the hemoglobin content is not greatly diminished.

In tables 4 and 5, the blood studies of 2 specimen families are recorded, demonstrating the incidence of the mild and severe forms, respectively. In the family of F. R. (table 4), the father (F. R.) and 1 daughter (J. R.) were unaffected, while the mother and 4 children (M. R., F. R., V. R. and M. R.) revealed evidences of the mild disease. Despite continued antianemia therapy, the blood levels, the morphologic abnormalities in the blood smears and the response to the fragility test remained unaltered. In the family of J. P. (table 5), both parents (J. P. and C. P.) and 1 child (P. P.) were affected with the mild disease and 3 children (R. P., J. P. and T. P.) had the advanced form requiring periodic blood transfusions.

TABLE 5.—*Blood Studies in Family of J. P., With the Severe Form of Mediterranean Anemia**

	Father J.P.	Mother C.P.	Patient P.P.	Patient R.P.	Patient [illegible]	Patient T.P.
Age, yr.	39	34	11½	10	8	4
Hemoglobin, Gm.	12	11	11.5	7.5	8.5	7.5
Red cells, millions	5.51	5.39	5.45	3.2	3.8	2.9
Hematocrit, per cent	41	38	38	25	29	25
Mean red cell volume, cubic microns	74	71	70	78	[illegible]	86
Hemoglobin concentration in red cells, per cent	29	29	30	30	[illegible]	30
Stippling	+++	++	++	+++	++	++
Hypochromic macrocytes	++	++	+	+++	+++	++
Target cells	+	+	++	++	+	++
Oval cells	+	++	++	++	+	++
Icteric index	7.5	6.8	6.8	37	14	16
Reticulocytes, per cent	5	3	4	....	6	3.1
Nucleated red cells per 100 white cells	0	0	0	12	0	14
Fragility Test						
Hemolysis begins	0.425	0.4	0.375	0.4	0.4	0.5
Hemolysis ends	0.25	0.25	0.25	0.225	0.2	0.15

*Note that the father, J. P., the mother, C. P., and 1 daughter, P. P., reveal hematologic evidences of the mild form of the disease. Three children, R. P., J. P., and T. P., have the advanced form requiring periodic transfusions. In every family thus far studied with 1 or more severely anemic children, as in this one, both parents bear the trait for the disease.

INEFFECTIVENESS OF IRON THERAPY

The present study substantiated previous observations that all forms of antianemia therapy, with the exception of transfusions, failed to elevate the hemoglobin or hematocrit values or otherwise to alter the blood picture in Mediterranean anemia. Many of the children with the mild form of the disease were treated initially with a variety of iron preparations because of lowered hemoglobin values attributed to nutritional anemia. The ineffectiveness of iron therapy for these children led to the investigation of the blood of siblings and parents with the frequent discovery of the familial incidence of Mediterranean anemia.

As a general rule, the absence of a reticulocyte response and the lack of regeneration of hemoglobin in approximately three to four weeks after the administration of an iron salt in sufficient dosage (such as 6

to 8 grains [0.39 to 0.52 Gm.] of ferrous sulfate daily) suggest that the diagnosis of nutritional anemia is to be questioned and that Mediterranean anemia is to be suspected. Similarly for an adult, the diagnosis of this disease should be entertained for persons of Italian or Greek origin with a mild or moderate anemia which has been refractory to the established forms of antianemia therapy.

HEREDITARY TRANSMISSION

Analysis of the 47 families in figures 6, 7 and 8 substantiates previous studies concerning the high incidence of transmission of the disease from parent to offspring. It will be noted that in every instance in which an affected child was recognized, qualitatively similar abnormalities of the blood were also discovered in at least 1 parent. In 35 of the 47 families there was an opportunity to examine the blood of both parents. Children with the advanced and mild forms of the disease were observed in 16 of the families (fig. 6), and in 19 families (fig. 7), the milder types occurred exclusively. Examination of figure 6 reveals the significant fact that in every family with a severely anemic child both parents bore the trait for the disease. It had been pointed out in another paper that incomplete studies in 1 family (fig. 6, family A. G.) might prove an exception to this law of inheritance. Subsequent studies, however, have demonstrated unequivocally that the mother, who had been regarded as normal, was also a carrier of the disease.

These genetic relationships justify the addition of another diagnostic criterion to those already elaborated, namely, the occurrence of alterations in the blood in other members of the family similar to those of the affected child. Furthermore, from the consistent familial incidence summarized in these tables, it may be affirmed that the designation of a blood dyscrasia as Mediterranean anemia should not be made unless at least 1 of the parents shows the trait for the disease.

The clinical material is as yet too meager to warrant definite conclusions concerning the relation between rank in the family and incidence of the disease. Examination of figures 6 and 7 indicates, however, that in those instances in which both parents were carriers the first-born child might be normal, but all subsequent children had the disease in mild and severe form. The implications of the hypothesis that the birth of a child with Mediterranean anemia of any type to 2 affected parents precludes further offspring entirely free of the disease are far reaching. A larger body of data obviously must be collected and subjected to rigid statistical analysis before this principle can be accepted as universally true.

In this paper the diagnostic criteria have been formulated by which the asymptomatic heterozygote who carries the abnormal genes can be recognized. It has also been shown that except for the most

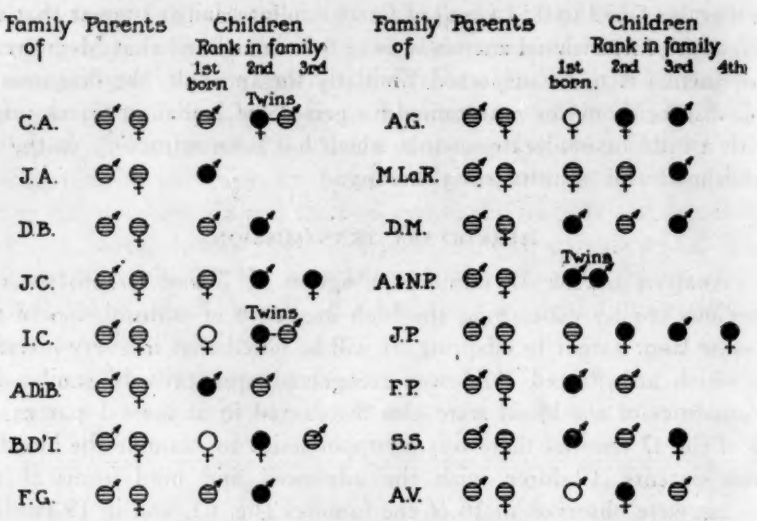

Fig. 6.—Heredity in advanced cases of Mediterranean anemia. Note that in every family with a severely anemic child both parents reveal the trait of the disease. White circles indicate normal children; cross hatching, trait or mild anemia; black circles, severe anemia, and circles with question marks, death with history of severe anemia.

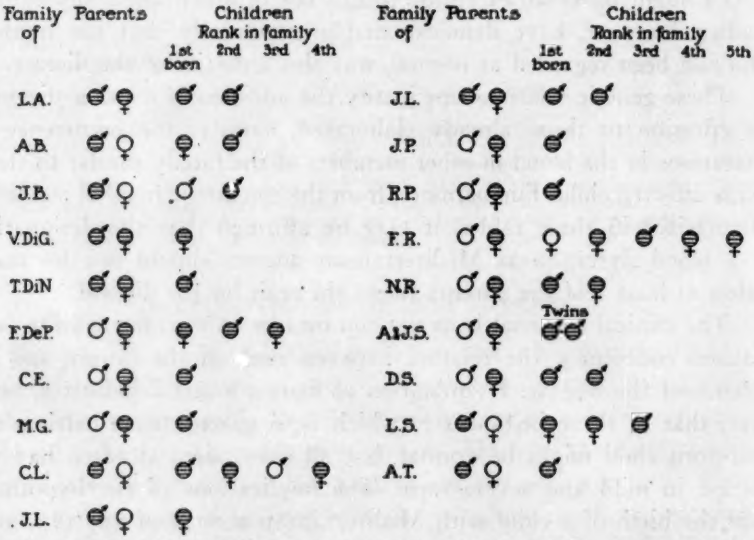

Fig. 7.—Note that in every family in which an affected child was detected similar abnormalities of the blood are present in at least one parent and frequently in other siblings. White circles indicate normal children and cross-hatched circles, trait or mild anemia.

The clinical and hematologic summaries of the family of A. B., F. DeP., M. G., F. R., A. and J. S. and D. S. in this figure; of I. C., A. DiB., D. M., A. and N. P., J. P. and S. S. in figure 6, and of J. A., C. A., A. C. and J. F. in figure 8 were reported in the previous study.[21]

severely anemic patient only 1 affected parent is required for transmission of the disease. Within the limitations of the available experience the present data reenforce the views previously expressed that Mediterranean anemia is transmitted on the basis of a dominant hereditary factor. In a later paper a genetic theory will be elaborated which will attempt to reconcile the controversial aspects of the hereditary mechanisms involved in this disease.

TERMINOLOGY

Soon after the original description of the severe form of this disease by Cooley and associates,[1] Whipple and Bradford[25] proposed the term "thalassemia," derived from the Greek word meaning the great sea,

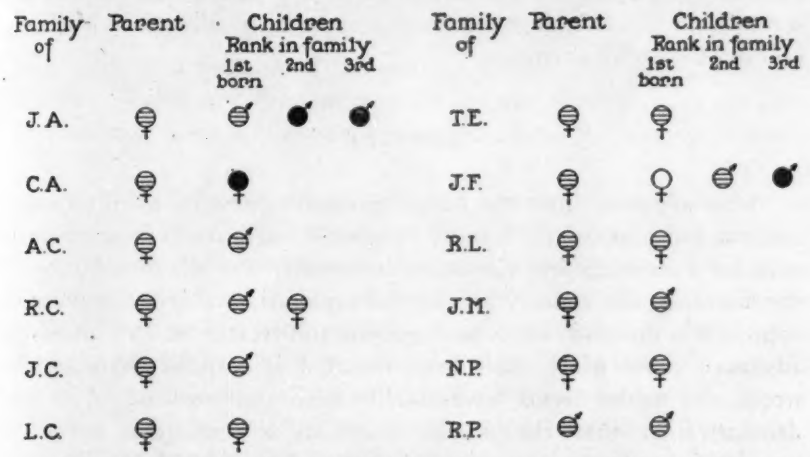

Fig. 8.—Heredity in families with mild and advanced forms of Mediterranean anemia in which one parent was examined. The presence of abnormalities of the blood in the single parent of each family emphasizes the frequency of the trait in asymptomatic persons. White circles indicate normal children; cross hatchings, trait or mild anemia; black circles, severe anemia, and circles with question marks, death with history of severe anemia.

which was used to designate the Mediterranean. The alternative term "Mediterranean disease" or "Mediterranean anemia" was also suggested as appropriate. In recent years there has been a growing tendency to refer to the disease by the English term, rather than by its Greek derivative. It should be pointed out that if "thalassa" refers to the Mediterranean Sea, the anemia associated with it should be referred to more properly as "thalassanemia" rather than "thalassemia."[26]

25. Whipple, G. H., and Bradford, W. L.: Racial or Familial Anemia of Children Associated with Fundamental Disturbances of Bone and Pigment Metabolism (Cooley-Von Jaksch), Am. J. Dis. Child. **44**:336-365 (Aug.) 1932.

26. Nittis, S.: Personal communication.

There are other objections to reviving the term "thalassemia." It has been shown in the present paper that every gradation of severity is encountered in this disease from the mildest form without anemia to the advanced types requiring transfusions (table 2). It is possible in accordance with the concept of Valentine and Neel[2j] to designate the conditions at either extreme as "thalassemia minor" and "thalassemia major," respectively. There is, however, a large intermediate group which includes the less severe type of the full-blown disease and the severer form of the mild type to which these terms do not strictly apply. To avoid confusion and the burden of excessive terminology, it seems more suitable to maintain the English designation of Mediterranean anemia and to qualify each case as mild, moderate or severe. Since to Thomas Cooley goes the credit of discovery of this disease, the severe form which he first described may be distinguished as Mediterranean (Cooley's) anemia.

COMMENT

It is apparent from the foregoing observations of Mediterranean anemia, and particularly from their genetic implications, that there is need for a thorough and systematic investigation of the distribution of the disease in this country and for the exploration of newer avenues of approach in the study of its pathogenesis and treatment. In contrast to advanced cases which have been reported in various parts of the world, the milder forms have usually been unrecognized. With the demonstration that the disease manifests a continuous range of severity from the asymptomatic individual form with the trait to the overt type, Mediterranean anemia assumes the magnitude of the other hereditary hemolytic syndromes. The broadening concept of Mediterranean anemia, since the initial phase when the severe form was described by Cooley, has been well summarized in a recent paper by Wolman and Dickstein.[27]

With the aid of the diagnostic criteria set forth in the present paper, it has been demonstrated that persons bearing the trait for Mediterranean anemia are surprisingly common in New York city. If this experience and that of another city[3] can be duplicated elsewhere, the importance of this disease can be recognized in the United States, where there are over 5,000,000 susceptible persons. Mediterranean anemia is of concern to the internist, as well as to the pediatrician, for the adult serves not only as a carrier but may also have a moderate

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27. Wolman, I. J., and Dickstein, B.: Changing Concepts in Mediterranean (Cooley's) Anemia, Am. J. M. Sc. **212**:723-737 (Dec.) 1946.

form of this disease, which is frequently incorrectly diagnosed and treated.

It was pointed out that the reason for recognizing asymptomatic persons who possess the trait is that they represent the carriers of the abnormal genes and therefore constitute the potential source of its transmission. The observations presented in this paper support the two hereditary principles previously expressed that in no family with an affected child were both parents free from the disease and that in every family with a child with severe anemia both parents revealed abnormalities of the blood. It is obvious that there is need for caution in applying these results, since the restriction of advanced cases to families with 2 affected parents carries important implications that necessitate further investigation and more conclusive proof. It is essential in this group to investigate nongenetic, as well as strictly genetic, factors because of the striking difference between the small number of reported cases of severely anemic children and the great frequency of marriages among persons in whom the trait is relatively common.

Despite these limitations, the fact remains that Mediterranean anemia involves a hereditary defect for which no specific treatment is as yet available, so that the problem of controlling the spread of the disease, particularly in its advanced form, depends ultimately on eugenic control. The need for exhaustive examination of the blood of both parents cannot be overemphasized when advice is sought concerning the likelihood of the severe type of disease in future pregnancies. There is every indication that Mediterranean anemia will provide a striking opportunity for furnishing genetic information of this sort because it is possible by appropriate laboratory measures to differentiate the carrier from the normal person. This study also suggests the advisability of reinvestigating the transmission of other members of the hemolytic group—sickle cell anemia and congenital hemolytic jaundice —to determine whether the mild and severe forms of these diseases follow a hereditary pattern similar to that of Mediterranean anemia.

It should be emphasized that the conclusions drawn from the data reported in this paper must be appraised with the reservations imposed by the small segment of the population included in this study. No true estimate of the frequency of this disease can be obtained from the data provided by this or any other study as yet reported, since families have been examined not at random but because of the detection of affected children. With more extensive data, genetic theories can be more thoroughly tested and the hereditary mechanisms involved in transmission elucidated.

The present study indicates that it might be profitable to investigate the various forms of Mediterranean anemia in the European

countries in which it originates. It is possible that those parts of the world beyond the geographic limits of the Mediterranean from which severe cases have been reported may prove on further study to represent foci of the disease. The discovery of carriers of Mediterranean anemia in these and in other areas may serve as an additional technic for carrying out anthropologic studies. By tracing the distribution and migration of affected races, it is conceivable that the earliest origins of this disease will be more accurately determined.

SUMMARY

This study based on the results of examinations of the blood of 181 persons in 47 families with Mediterranean anemia (familial erythroblastic anemia) demonstrates the frequency of the mild form of this disease. The susceptible population in this country consists of over 5,000,000 persons of Mediterranean origin, and, from the experience in New York city, the disease in mild form is probably prevalent in other comparable communities.

While advanced forms of Mediterranean (Cooley's) anemia are readily diagnosed, the milder form is usually overlooked. The importance of detecting asymptomatic persons who bear the trait for the disease is that they constitute a potential source of the hereditary transmission of the disease in any of its clinical forms. Mediterranean anemia is of concern to the internist, as well as to the pediatrician, for the adult serves not only as a carrier, but may also have a moderate form of this disease, which is frequently incorrectly diagnosed and treated.

Diagnostic criteria are described by which the mild form of the disease can be recognized. Hematologic procedures were adapted to screen out persons with Mediterranean anemia of all grades of severity from large groups of patients.

While the roentgenographic changes and marked clinical manifestations that characterize the severe form of Cooley's anemia are absent in the person with the mild form of the disease, the changes in the blood are distinctive and readily demonstrable. In these persons polycythemia may occur, with normal or lowered hemoglobin levels, and basophilic stippling may be sufficiently pronounced to suggest lead posioning. One of the more important diagnostic features is the occurrence of alterations in the blood in healthy members of the family similar to those of the affected child.

The data presented in this paper support the hereditary principles that in no family with an affected child were both parents free from the disease and that in every case of a severely anemic child requiring

periodic transfusions both parents revealed abnormalities of the blood. In every one of the 16 families with a severely anemic child both parents bore the trait for the disease. Since appropriate laboratory procedures permit the differentiation of the carrier from the normal person, it may be possible with more extensive experience to furnish genetic information concerning the likelihood of the occurrence of the severe type of this disease in future pregnancies.

Several cases of the advanced form of Mediterranean anemia have been reported from parts of the world beyond the limits of the Mediterranean. It is suggested that the detection of hematologic abnormalities in asymptomatic persons with the mild form of the disease may serve as an additional technic for carrying out anthropologic studies and for determining more precisely the earliest origins of this disease.

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ROOTING REFLEX IN THE NEWBORN INFANT: INCIDENCE AND EFFECT ON IT OF SLEEP

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THE HEALTH of the newborn infant depends on an adequate intake of nourishment shortly after he becomes independent of his mother. Therefore, it is of importance to study the various activities which constitute suckling behavior. At the touch of the nipple (1) the infant's lips open; his lower jaw drops so that the nipple can enter his mouth; his lips close about the nipple, and (2) he begins to suck. If this results in the flow of milk or water, he swallows. In addition to the activities just described, there are other specific types of behavior which are said to be related to suckling. One of these types, which is called the "rooting reflex," has been selected for study in addition to the first two acts of suckling: (1) the behavior of the infant's lips when brought into contact with the nipple and (2) actual sucking.

PURPOSE OF THE STUDY

Our purpose was to find out whether every baby is born with the ability to perform the rooting reflex and, if not, to determine what the factors are which influence its occurrence. The factors studied were age, hunger, satiety and wakefulness. The term "wakefulness" is used to include all gradations observed, from deep sleep to wide-awakeness.

SUBJECTS

The subjects were 71 healthy newborn infants, each of whom weighed 2,500 Gm. or more. They were observed every day during their neonatal period of eight to ten days in the hospital.

From Section on Pediatrics, Mayo Clinic (Dr. Aldrich).

METHOD

General Considerations.—The time of day selected for observation was as close to feeding time as possible, varying from thirty to forty-five minutes. All infants were observed before feeding time, and in addition approximately one third of them also were observed after they had been fed. They remained in their cribs in the sleeping part of the nursery while being tested. This was a room separate from that in which examinations and other procedures were carried out.

The majority of the infants were fed on a four hour schedule, most of them at the breast. Those who were fed from a bottle were given it by the mother, as a rule.

Evaluation of Sleep or Wakefulness.—At the first approach to the infant, notice was taken as to his state of wakefulness. If he was crying, it was obvious that he was awake. If he was not crying, he was observed for one minute before judgment was made. In the last half of the study an attempt was made to distinguish depth of sleep also. With some revision of Wagner's[1] gradations of depth of sleep, six classifications were made, ranging from deep sleep to full wakefulness:

1. "Deep sleep" was taken to mean closed eyelids with no observable movement whatever except respiration.

2. "Light sleep" denoted closed eyelids and two of the following: one or two movements of body, eyelids or mouth.

3. "Dozing" was assumed to consist of closed eyelids, with more general or more frequent body movements, often associated with movements of the eyelids and mouth.

4. "Sleepy" characterized a state in which the eyelids were opening and closing or were partly open and the eyes had a "sleepy" look.

5. "Awake and not crying" signified eyelids constantly open and eyes with an alert expression, a state usually associated with active general body movement.

6. "Crying" referred to eyelids open or closed, usually the latter, always associated with active general body movement.

ROOTING REFLEX

When the cheek of an infant is stimulated by either constant or moving light pressure of a person's finger, the baby turns his head toward the finger and opens his mouth. This is the rooting reflex. The act of opening the mouth is an essential part of this activity, which distinguishes it from three other side to side movements that may be confused easily with the rooting reflex. The three movements in question are: (1) the so-called random side to side movement of the head, often associated with other bodily activity seen during the waking state, (2) the turning of the head toward the "preferred" side and (3) the turning of the head either toward or away from the presenting finger without opening the mouth. The first two movements are not evoked in response to the finger, whereas the third is. The third movement, however, is not the rooting reflex, because it is not directed at securing the finger.

Inasmuch as a baby less than 2 months of age commonly lies on a preferred side of the head, the head of the child under observation was

1. Wagner, I. F.: The Establishment of a Criterion of Depth of Sleep in the Newborn Infant, J. Genet. Psychol. **51**:17-59, 1937.

always placed so that he was "looking" straight forward, in order that both sides of his face could be tested. If the baby was crying, he was pacified prior to testing by patting him or sitting him up, so that he would close his mouth and stop all vigorous movements of the head.

With the tip of the tester's finger, steady, light pressure was applied to the cheek of the infant approximately one-half inch lateral to the angle of the lips. If no reflex occurred within five seconds, this steady pressure was replaced with a to and fro movement with the same degree of pressure, care being taken not to touch the lips of the infant. The finger was moved to and fro seven times before contact was broken, unless the reflex occurred before the seven strokes had been completed. This was done to both cheeks.

Tactile Stimulation of the Lips.—A dry rubber nipple was touched to the lips of the infant, and notice was taken of whether he opened his mouth or made labial movements.

SUCKING BEHAVIOR

The test for the rooting reflex always preceded the use of the nipple for determination of sucking behavior. Sucking, or the absence of it, was observed after the nipple had been placed in the mouth of the infant. Sucking, or the absence of it, was rated in four ways: 0, failure of the infant to make any movements of the lips or mouth; 1, movements of the lips or tongue which could be described as "mouthing," consisting of opening and closing the lips, or licking and pushing movements by the tongue; 2, actual sucking movements which were few in number with long pauses between them, usually necessitating disturbance of the infant by some kind of stimulation to obtain continued sucking; 3, a series of a few sucks at a time with short pauses, or continuous sucking without pauses, totaling at least twenty-five sucking movements. This was satisfactory sucking.

Awakening the Infant.—If the rooting reflex was not obtained and if the baby was not crying at the time testing was initiated, attempts were made to awaken the baby. After each attempt, the infant was tested for the reflex. A definite routine for awakening him was carried out. It was comprised of the following steps: (1) turning him over if he was lying prone, (2) vigorously rubbing him on the chest and abdomen, (3) sitting him up and rubbing him vigorously and (4) compressing his large toe between thumb and forefinger in an effort to induce crying. This last-named maneuver consisted of firm pressure and was in no sense pinching. Maneuvers 3 and 4 were repeated twice, and testing followed each repetition. If the child was judged to be deeply asleep initially, usually all these maneuvers were necessary.

RESULTS

Except where otherwise specified, all the data reported in the present study were obtained from infants tested before they had been fed. All the titles, "asleep," "awake and not crying" and "crying," in the tables and the figures refer to the state of the infant when testing began. Therefore, the state of wakefulness of the baby at the time the reflex was obtained was usually different from the original state, for testing followed a procedure of awakening.

Rooting Reflex.—The rooting reflex was manifested by every one of the infants at one time or another. We observed it to be influenced

TABLE 1.—*Effect of Sucking on a Nipple on the Incidence of the Rooting Reflex (Just Before Feeding)*

State of Wakefulness	Observations, Total Number	Reflex Elicited: Before Sucking, Number	Before Sucking, Per Cent	After Sucking, Number	After Sucking, Per Cent
Deep sleep	16	2	12.5	9	56.2
Light sleep or dozing	69	40	58.0	50	72.4
Awake and not crying	83	53	63.8	72	86.7
Crying	85	70	82.3	76	89.4
Total	253	165	65.2	207	81.8
Awake and not crying and crying	168	123	73.2	148	88.1

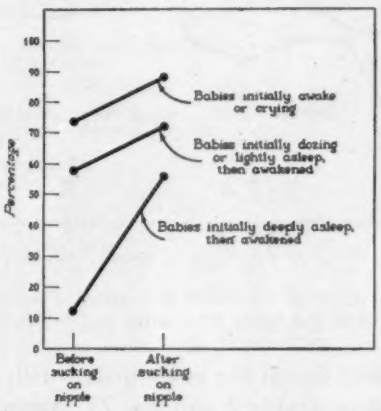
Babies initially awake or crying
Babies initially dozing or lightly asleep, then awakened
Babies initially deeply asleep, then awakened
Percentage
Before sucking on nipple
After sucking on nipple

Fig. 1.—The effect, on elicitation of the rooting reflex, of sucking on a nipple. The infants represented in this figure were tested just before they were fed.

by at least four factors: (1) the state of wakefulness, (2) sucking behavior, (3) age and (4) whether or not the infant had been fed. These four factors will be considered next.

State of Wakefulness: Three different states of wakefulness could be distinguished on the basis of the incidence of the rooting reflex: (1) deep sleep, (2) light sleep or dozing and (3) awakeness, whether the infant was crying or not (table 1 and fig. 1). Inasmuch as all babies deeply asleep or dozing did not manifest the rooting reflex and had to be awakened in every case before it was seen, the factor that was being tested actually consisted of how much one can arouse babies who are asleep. Even after they had been awakened, of the 16 infants initially

deeply asleep, only 2, or 12.5 per cent, exhibited the rooting reflex, whereas 73.2 per cent of those initially wide awake, whether or not they were crying, exhibited the reflex (table 1).

Sucking Behavior: When the baby was retested for the rooting reflex after he had sucked on the dry rubber nipple, the percentage of reflexes elicited was decidedly increased. In table 1 and figure 1 are shown the effects of sucking behavior on elicitation of the reflex. Among the infants who initially had been deeply asleep, the percentage occurrence of the reflex in question increased from 12.5 before sucking to 56.2 after sucking. The act of sucking also had a definite influence on occurrence of the reflex among lightly sleeping infants and infants awake and not crying, but it had little, if any, influence on occurrence of the reflex among crying babies.

Age: The third factor which influenced manifestation of the rooting reflex was age. This was strikingly apparent on the basis of observa-

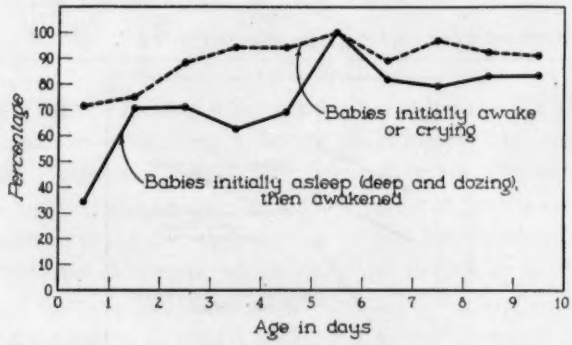

Fig. 2.—The factor of age of the infant in relation to the incidence of the rooting reflex. Infants represented in this figure were tested just before they were fed.

tions made on the first day of life as compared with observations made on all succeeding days (table 2 and fig. 2). Again, these figures are most significant when the fact of whether the infant was originally awake or asleep is considered. On the first day the percentage of infants initially asleep and then aroused who exhibited the reflex was only 34.6 (table 2). During the next four days this percentage increased to a height which appeared to be fairly constant. This constancy was maintained at a somewhat higher figure during the last four days, if the figure for the sixth day is ignored. In figure 2 are shown these two percentile levels after the initial low point. The incidence of the reflex among the infants who were awake or crying at the time they were tested was lower during the first two days after birth and then remained about the same for the rest of the time.

When we examined the charts of individual infants to ascertain the day on which the rooting reflex was first manifested, regardless of the

TABLE 2.—*Incidence of the Rooting Reflex as Related to the Day of Age (Just Before Feeding)*

State of Wakefulness	First Day			Second Day			Third Day			Fourth Day			Fifth Day		
	Observations, Total No.	Reflex Present Number	Reflex Present Per Cent	Observations, Total No.	Reflex Present Number	Reflex Present Per Cent	Observations, Total No.	Reflex Present Number	Reflex Present Per Cent	Observations, Total No.	Reflex Present Number	Reflex Present Per Cent	Observations, Total No.	Reflex Present Number	Reflex Present Per Cent
Asleep	26	10	34.6	24	17	70.8	21	15	71.4	24	15	62.5	26	18	69.2
Awake and not crying	17	13	76.5	15	11	73.3	18	17	94.4	15	14	93.3	10	10	100
Crying	4	2	50.0	13	10	76.9	16	13	81.2	20	19	95.0	25	23	92.0
Total	47	25	53.2	52	38	73.1	55	45	81.8	59	48	81.3	61	51	83.6
Awake and crying	21	15	71.4	28	21	75.0	34	30	88.2	35	33	94.2	35	33	94.2

State of Wakefulness	Sixth Day			Seventh Day			Eighth Day			Ninth Day			Tenth Day		
	Observations, Total No.	Reflex Present Number	Reflex Present Per Cent	Observations, Total No.	Reflex Present Number	Reflex Present Per Cent	Observations, Total No.	Reflex Present Number	Reflex Present Per Cent	Observations, Total No.	Reflex Present Number	Reflex Present Per Cent	Observations, Total No.	Reflex Present Number	Reflex Present Per Cent
Asleep	14	14	100	22	18	81.8	24	19	79.1	18	15	83.3	6	5	83.3
Awake and not crying	12	12	100	13	11	84.6	11	11	100	6	5	83.3	4	3	75.0
Crying	33	33	100	24	24	100	20	19	95.0	7	7	100	7	7	100
Total	59	59	100	59	53	89.8	55	49	89.1	31	27	87.1	17	15	88.2
Awake and crying	45	45	100	37	35	89.1	31	30	96.8	13	12	92.3	11	10	90.9

Observations, Grand Total

	Total Observations	Reflex Present, No. of Observations	Reflex Present, Per Cent of Observations
Asleep	215	146	67.9
Awake and not crying	121	107	88.4
Crying	169	157	92.9
Total	505	410	81.2

*Of observations.

state of wakefulness, we observed that, of the 71 babies the reflex was exhibited in 31, or 43.7 per cent, the first day; 55, or 77.4 per cent, within the first two days; 62, or 87.3 per cent, within the first three days; 65, or 91.5 per cent, within the first four days; 67, or 94.4 per cent, within the first five days, and 71, or 100 per cent, within the first six days.

TABLE 3.—*Sucking Related to Age (Just Before Feeding)*

State of Wakefulness	Total Observations	First Day Rating 0	1 and 1 to 2	2 and 2 to 3	3	Per Cent 3	Total Observations	Second Day Rating 0	1 and 1 to 2	2 and 2 to 3	3	Per Cent 3
Asleep	26	3	4	8	11	42.3	20	..	..	1	19	95.0
Awake or crying	21	..	2	..	19	90.5	27	..	1	4	22	81.5
Total	47	3	6	8	30	63.8	47	..	1	5	41	87.2
		Third Day						Fourth Day				
Asleep	19	1	..	2	16	84.2	19	..	..	6	13	68.4
Awake or crying	32	..	..	..	32	100	32	..	..	1	31	96.9
Total	51	1	..	2	48	94.1	51	..	..	7	44	86.3
		Fifth Day						Sixth Day				
Asleep	21	..	..	7	14	66.7	12	..	..	1	11	91.7
Awake or crying	32	..	..	..	32	100	44	..	..	..	44	100
Total	53	..	..	7	46	86.8	56	..	..	1	55	98.2
		Seventh Day						Eighth Day				
Asleep	22	..	1	3	18	81.8	21	..	..	3	18	85.7
Awake or crying	36	..	1	1	34	94.4	31	..	..	..	31	100
Total	58	..	2	4	52	89.7	52	..	..	3	49	94.2
		Ninth Day						Tenth Day				
Asleep	17	..	..	2	15	88.2	5	..	..	1	4	80.0
Awake or crying	10	..	..	1	9	90.0	10	..	..	..	10	100
Total	27	..	..	3	24	88.9	15	..	..	1	14	93.3

		Grand Totals										
							Observations 3					Per Cent 3
Asleep	182	4	5	34	139	76.4	43	..	..	..	..	23.6
Awake or crying	275	..	4	7	264	96.0	11	..	..	..	..	4.0
Grand Totals	457	4	9	41	403	88.2	54	..	..	..	..	11.8

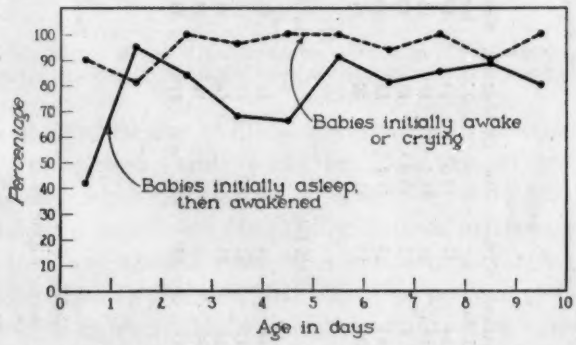

Fig. 3.—The relation of age of the infant to satisfactory sucking.

Intake of Food: The fourth factor which influenced the incidence of the rooting reflex was the intake of food. Of the 55 observations made on babies who had just eaten, 41.8 per cent resulted in elicitation of the reflex.

Tactile Stimulation of the Lips.—When the rubber nipple was touched to the lips of an infant who was wide awake, the lips opened

and the nipple slipped into his mouth. In 87 observations there were 26 failures to open the lips, but all except 4 of these failures were noted in sleeping babies or in babies who initially had been asleep and were then wakened. The distribution of sleeping infants who did not open their mouths on tactile stimulation of the lips was the same throughout the period of hospitalization.

Sucking.—Sucking is influenced by wakefulness, age and intake of food, but to a somewhat lesser degree than the rooting reflex is (table 3 and fig. 3).

Of 457 observations of sucking behavior, 403, or 88.1 per cent, pertained to satisfactory sucking. Two thirds of the infants who did not suck satisfactorily were less than 2 days old. Three of the 4 infants who refused to make mouth or lip movements of any kind when the nipple was placed in their mouths were less than 1 day old. After the first two days, 100 per cent of those infants who were initially awake when they were tested sucked satisfactorily and 72 per cent of those who were initially asleep at the times they were tested also sucked satisfactorily (fig. 3).

RELATION OF THE ROOTING REFLEX TO SATISFACTORY SUCKING

Infants who sucked unsatisfactorily and who lacked the rooting reflex were more frequently less than 1 day of age than any other age.

The rooting reflex was manifested in 86.5 per cent of 334 instances of satisfactory sucking on the test nipple. Satisfactory sucking on the test nipple was present in 96 per cent of 300 instances in which the rooting reflex was elicited.

Infants who were awakened from sleep were more likely to suck satisfactorily than to exhibit the rooting reflex. Of infants initially deeply asleep at the time of testing and then awakened, 73.7 per cent sucked satisfactorily on the nipple and 56.2 per cent exhibited the rooting reflex.

COMMENT

Rooting Reflex.—The behavior which has been called the "rooting reflex" was described by Gesell and Ilg,[2] Blanton,[3] Jensen,[4] Dennis[5] and Pratt, Nelson and Kuo Hua Sun,[6] but none of these authors

2. Gesell, A., and Ilg, F.: Feeding Behavior of Infants: A Pediatric Approach to the Mental Hygiene of Early Life, Philadelphia, J. B. Lippincott Company, 1937, pp. 16 and 75.

3. Blanton, M. G.: The Behavior of the Human Infant During the First Thirty Days of Life, Psychol. Rev. **24**:456-483, 1917.

4. Jensen, K.: Differential Reactions to Taste and Temperature Stimuli in Newborn Infants, Genetic Psychology Monographs, Worcester, Mass., Clark University Press, 1932, vol. 12, nos. 3 and 4, pp. 361-479.

5. Dennis, W.: A. Description and Classification of the Responses of the Newborn Infant, Psychol. Bull. **31**:5-22, 1934.

6. Pratt, K. C.; Nelson, A. K., and Kuo Hua Sun: The Behavior of the Newborn Infant, Columbus, Ohio, Ohio State University Press, 1930.

mentioned opening of the mouth as a part of the reflex. Pratt and associates attributed the first description of the reflex to Samuel Pepys, who, in 1667, wrote in his "Diary": "They tell me what I did not know that a child (as this do) will hunt up and down with its mouth if you touch the cheek of it with your finger's end for a nipple, and fit its mouth for sucking."[7] Buehler and Hetzer[8] included this reflex in their series of tests for the first month of the infant's life, but they included in their definition sucking movements of the lips or opening of the mouth. They also wrote that the infant's head turns toward or away from the experimenter's hand. We do not remember seeing any infant who turned away from the stimulus and opened his mouth.

The significance of the rooting reflex lies in the fact that the touch of the mother's breast to the cheek of the child will cause him to turn his head and open his mouth to receive the nipple.

It is possible that the rooting reflex which occurs after sucking on the nipple is different from that which occurs before sucking. It might be the result of anticipation of further sucking as described by Gesell and Ilg. They state:

> When turned to the nursing position he [the newborn infant] may promptly begin to turn his head from side to side in a searching manner . . . . he may not make an adaptive approach upon the nipple until it is touched to his mouth. . . . Although he does not poise his lips on the presentation of the first breast, he makes this adaptive approach on the second breast even in his drowsiness.

Buehler and Hetzer observed that if the feeding is interrupted after a few minutes the infant moves his head toward the breast or bottle and tries to grasp it again with the open mouth. (We saw this reaction, also, on eight or ten occasions when the nipple was removed from the baby's mouth.) We believe that the interpretation of anticipation for the rooting reflex behavior after sucking is justified because this reflex was usually obtained immediately after stimulation by the finger, whereas when an infant was tested before sucking the reflex was obtained in many instances only after delay or not at all.

Another possible explanation of the fact that the act of sucking induced a higher percentage of occurrence of the rooting reflex in our subjects is that sucking acts as a stimulant or a reenforcement in some way, perhaps also on a basis of anticipation. This is suggested by the fact that the stimulating effect was greater in the baby awakened from sleep than in the one awake and not crying and was absent in the one who was crying (fig. 1).

Pratt and associates and Dennis wrote that the rooting reflex was manifested by an infant a few hours old. We elicited it from a baby

7. Pepys, S., cited by Pratt, Nelson, and Kuo Hua Sun.[6]

8. Buehler, C., and Hetzer, H.: Testing Children's Development from Birth to School Age, translated by H. Beaumont, New York, Farrar & Rinehart, Inc., 1935, pp. 95-97.

½ hour old and from another 1 hour old. Of the 13 babies tested before they were 6 hours old, 8, or 61.5 per cent, manifested the rooting reflex.

Tactile Stimulation of the Lips.—Ford,[9] Dennis, and Gesell and Ilg described the opening of the infant's lips on contact with the nipple. The response is a reflex which is important in the act of sucking, for it is necessary for the reception of the nipple.

Nurses who care for newborn infants frequently depress the chin of the infants who refuse to open their mouths when the nipple touches their lips. We wished to learn whether this maneuver is necessary only in the feeding of sleepy babies or whether it is needed because of developmental absence of the reflex. The fact that 22 of 26 failures to open the mouth were noted in babies who were awakened from sleep seems to suggest that drowsiness is the important factor. In fact, we observed time and again that when we aroused the infant he opened his lips to the touch of the nipple, whereas while he was asleep he did not do so.

The infant was less willing to open his mouth after he had been fed; hence, it was necessary to depress his chin oftener so that his mouth would receive the nipple. Jensen referred to this as being one of the reactions to satiety. (We must, however, add that we were not so thorough nor so vigorous in our attempt to awaken the child who had just been fed as in that to awaken the one who had not.)

Sucking Behavior.—When a method of rating sucking behavior was set up, it was observed that without some measure of effectiveness, such as the amount and rate of intake of milk or water or the degree of force involved in the act of sucking, further discrimination was impossible within the category we rated "sucking"[3] or "satisfactory sucking." Jensen[4] measured the pressure involved in the process of sucking and observed that the differences in pressure among infants were greater than the differences from one time to the next in the same infant. He described three different types of sucking reactions, all of which are included in our rating 3. He did not evaluate them in terms of effectiveness, but he did say that the most vigorous and long-continued sucking is done by hungry, awake babies.

We hoped that by use of a rubber nipple as a standard stimulus to sucking it would be possible to isolate infant factors which entered into either satisfactory or unsatisfactory sucking behavior. Inasmuch as only 11.8 per cent of the babies did not suck well on the nipple, it is obvious that most of them were born with this type of behavior fairly well coordinated. Of the 11.8 per cent who did not suck satisfactorily, 79 per cent had been aroused from sleep before they were tested. Therefore, drowsiness appears to be a definite factor in reducing the effective-

9. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, Springfield, Ill., Charles C Thomas, Publisher, 1937, p. 49.

ness of this activity. However, the fact that half of those who sucked satisfactorily were 1 or 2 days old suggests a lack of practice effect or some deleterious factor or factors associated with birth among those who did not suck satisfactorily. The latter problem will be considered later.

We observed some of the same types of behavior in sleepy infants both before and after feeding that Jensen said are reactions to satiety. He wrote that it was often necessary to depress the infant's chin to allow the nipple to enter his mouth, but that once the nipple was in place the infant often sucked well. Apparently, the act of sucking has a lower threshold for its elicitation than has opening of the infant's lips to the touch of the nipple. Jensen also described long pauses between sucks and disorganization of the sucking response necessitating stimulation. Because satiety usually is associated with falling asleep in the newborn infant, this behavior in both situations may be due to sleepiness and not to satiety.

Wakefulness.—Although our purpose was to study reflex and other behavior that might be related to the act of sucking or to the taking of nourishment, we found that we were studying various states of wakefulness as well. The extreme difficulty we experienced in trying to arouse or to awaken some of the infants, so that they would suck, was surprising. It was especially astonishing when it is remembered that the testing was done no more than forty-five minutes before the next feeding period, when presumably the infant should have been hungry. In several cases we carried out the entire routine of stimulation outlined previously, but even so, we did not succeed in awakening the infant. The extreme drowsiness of these infants is further confirmed by the fact that they fell asleep immediately when we ceased to stimulate them. This recalls to anyone who has worked with newborn infants the frequent complaint of mothers in the hospital that they are unable to awaken their babies so that they will nurse.

When we analyzed our data in search of factors which might have some relation to the lower incidence of the rooting reflex and satisfactory sucking in the first few days after birth of the infant, we were unable to determine that size of the baby, duration of the mother's labor, anesthetic agent administered to the mother or type of delivery had anything to do with it.

Is it possible that babies sleep more in the first day or two of life after birth? We made no attempt to analyze this problem. Inasmuch as motility entered into our judgment of the depth of sleep, reference to workers who studied motility should throw some light on this point.

Irwin and Weiss[10] and Pratt and associates studied motility during the first day of the neonatal period and arrived at opposing results.

Gesell and Amatruda[11] and Buehler[12] studied sleep in newborn infants for twenty-four hours a day. Both their reports mentioned the fact that even when the newborn infant seems most awake the quality of the wakefulness is not the same sort of alertness he later attains. There is a developmental aspect to the quality, as well as to the quantity, of wakefulness behavior, just as there is in other types of behavior.

Inasmuch, then, as the newborn infant awake is less responsive than he will become later, it would seem to be indicated that those who care for him should take advantage of his best period for feeding. On the basis of our experience with these infants, this period would seem to be the time at which the infant awakens spontaneously. If the most effective suckling behavior is to be obtained, then the feeding of the infant must be achieved according to a self-regulating schedule. The infant must be permitted to determine his own time of feeding. This time is in part synchronous with his waking schedule. He always awakens when he needs to eat, but he does not always need to eat when he awakens.

SUMMARY

The newborn infant when deeply asleep did not exhibit the rooting reflex, did not open his mouth to receive the nipple and did not suck on the nipple. Sometimes, after vigorous stimulation, he could be aroused to do all these things.

The infant who was dozing did not exhibit the rooting reflex and did not open his lips to receive the nipple. Sometimes he sucked on the nipple, but often he had to be stimulated to make him continue. Usually, he could be aroused so that he exhibited the rooting reflex, accepted the nipple when it touched his lips and sometimes sucked well.

The infant who was awake and was or was not crying usually manifested the rooting reflexes, opened his mouth readily to receive the nipple, unless he had just been fed, and sucked satisfactorily before a feeding and often after a feeding as well.

The most effective feeding behavior was exhibited by an infant after spontaneous awakening.

Rochester Child Health Institute (Dr. Aldrich).
Des Moines, Iowa (Dr. Gentry).

10. Irwin, O. C., and Weiss, A. P.: A Note on Mass Activity in Newborn Infants, Pedagog. Semin. **38**:20-28, 1930.

11. Gesell, A. L., and Amatruda, C. S.: Embryology of Behavior: The Beginnings of the Human Mind, New York, Harper & Brothers, 1945, pp. 144-159.

12. Buehler, C.: The First Year of Life, translated by P. Greenberg and R. Ripin, New York, The John Day Company, Inc., 1930, pp. 111-123 and 170-171.

PSYCHOLOGIC MANAGEMENT OF CHILDREN WITH GLOMERULAR NEPHRITIS

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DURING a two month period, 11 small children with edema due to the degenerative stage of glomerular nephritis were referred to the Clinic for Renal Disease of the Stanford University School of Medicine. Without exception, the care of these children was complicated by psychologic difficulties caused by unwarranted anxiety on the part of their parents. It is our purpose to discuss this problem and to suggest methods of prevention and treatment.

The anxiety of the parents uniformly arose as the result of fear and ignorance of the disease and its manifestations and from ill advised, and sometimes inaccurate, information obtained from physicians and from misinformation in the newspapers. Most of the parents firmly believed that the degenerative stage of glomerular nephritis with edema is invariably fatal. Many were told by physicians that no treatment is of use and were instructed merely to make their children comfortable until the end. Some children were ordered confined to their beds, and their physical activities were reduced to a minimum. Others were restricted from any contact with siblings or playmates on the grounds that they might become excited or contract infectious disease. In 1 case, the mother was instructed to stop all crying by her child, by whatever means necessary, so as to prevent an increase in periorbital edema. All the parents indulged in activities which could only have the effect of increasing their anxiety, without any actual profit to the children. One weighed her child three times daily, while another meticulously measured and charted each voiding of urine.

The overt anxiety thus induced in the parents naturally was observed by the children. The children soon learned that no parental discipline would be enforced and that all their desires would be granted. Therefore, a variety of psychologic manifestations soon became evident.

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Several children completely stopped walking, for they discovered that their parents would carry them. Other symptoms included irritability, emotional instability, refusal to eat, fickle appetite, vomiting, temper tantrums, wilfulness and insomnia. In short, the children were "completely spoiled." Not only is this sequence of events capable of severely disrupting the family group, but it also enormously complicates medical management.

Two illustrative cases follow:

CASE 1.—C. M., a girl 4 years of age, was referred to the clinic with the diagnosis of the degenerative stage of glomerular nephritis with ascites and edema. The edema was of two weeks' duration before referral.

When the child was first seen, the mother was agitated and tearful and related her fear that the child would soon be dead. She had read in the newspapers that nephritis with edema is always fatal, that the degree of edema is an indication of the proximity to death and that no useful treatment is known. She had withdrawn her child from all contact with playmates and had stopped any attempt at discipline, while she obediently served her child's demands.

Although the child had been reasonably well adjusted until the onset of edema, a large number of neurotic difficulties soon developed. She stopped walking and demanded that she be carried. Her appetite became capricious, and she drank so little liquid that her urinary output dropped to a dangerous level. Psychogenic vomiting became a serious problem, and she indulged in temper tantrums, crying and extreme wilfulness.

CASE 2.—H. L., a girl 3 years of age, whose diagnosis was the degenerative stage of glomerular nephritis, had edema of two months' duration before referral to the clinic.

On the first visit, the mother wept profusely. Her physician had told her that the child had an incurable disease for which no treatment was known. She had read in the newspapers of the "rare and dread disease nephrosis." She left home with her child and traveled about seeking a cure from various physicians, none of whom offered her hope. She weighed her child three times daily and measured and charted each voiding of urine. On advice from a physician, the activities of the child were reduced to a minimum.

No psychologic difficulties in the child were noticed prior to these events. Subsequently, however, she stopped walking and, at times, refused to stand. Insomnia, crying and wilfulness ensued, and maintaining adequate nutrition became difficult.

There is no need for these situations to arise, for the aforementioned notions are not in accord with the actual facts. The degenerative stage of glomerular nephritis is not an invariably fatal disease. In some cases the kidneys recover to the degree that they pass into the latent stage, and a few eventually heal completely.[1] There is no authoritative evidence to support the idea that treatment is of no avail. There is seldom a reason to order restriction of the child's activities or to treat him differently from other children. The child himself soon learns to regulate his activities in accordance with his physical capacity. The

1. Addis, T.: Glomerular Nephritis, New York, The Macmillan Company, 1948.

degree of edema is not of prognostic value; it has no relation to the status of the kidneys at the moment and, indeed, is nothing more than an unsightly and uncomfortable accumulation of extracellular fluid. The edema seldom becomes severe enough to warrant attempts to remove it. When this condition does occur, there is no need for undue alarm, for the fluid can be evacuated.

The treatment of any disease involves attention not only to the soma, but also to the psyche. This rule is particularly true of a chronic illness in children at an age when their emotional patterns are undergoing such rapid development. Every effort should be made to allow the child a normal emotional development in addition to adequate treatment of his renal lesion. We suggest, therefore, that some hope be offered, but that no definite prognosis be given. An attempt should be made to relieve the parents of unwarranted fears and to allay anxiety produced by popular misconceptions. Some parents should be warned specifically against revealing anxiety to their children. The children should be treated no differently from normal children of the same age. We recommend that the edema be considered as an obvious but transient hindrance and that efforts be made to prevent the child from using it as a symbol of illness.

It is our belief that the essential treatment for glomerular nephritis consists in the reduction of the work of the kidneys to a minimum.[2] This reduction is accomplished by maintaining a high urinary output and by restricting the protein intake to that adequate minimum required for maintenance and growth.[3] In addition, supplementary vitamins and calcium are prescribed to compensate for any possible deficit resulting from restriction of protein. When edema is present, the salt intake should be reduced. If the child refuses to eat without dietary salt, we compromise in regard to the salt intake, as it is more important to obtain good nutrition than to prevent formation of edema. These simple, positive measures are incorporated easily into the family routine. The child should not be led to think of them as setting him apart as an ill person.

An understanding by the parents of the disease and of the problems involved will largely prevent the inception of neurotic difficulties in their edematous children. Once such abnormalities have occurred, as in the 11 children discussed here, prompt improvement may be effected by a change in the attitudes and actions of the parents.

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2. Newburgh, J. D.: The Changes Which Alter Renal Osmotic Work, J. Clin. Investigation **22**:439-446, 1943. Borsook, H., and Winegarden, H. M.: The Work of the Kidney in the Production of Urine, Proc. Nat. Acad. Sc. **17**:3, 1931.

3. Addis, T.: The Treatment of Chronic Renal Insufficiency, J. Urol. **41**:126-136, 1939; The Osmotic Work of the Kidney and the Treatment of Glomerular Nephritis, Tr. A. Am. Physicians **55**:223-229, 1940.

SUMMARY

Children with edema due to the degenerative stage of glomerular nephritis frequently present behavior problems. The difficulties are discussed, and illustrative cases are presented.

These problems often are the result of parental anxiety based on unwarranted pessimism and misinformation.

They may be prevented and treated by a proper orientation of the parents toward the illness, a hopeful attitude on the part of the physician and a therapeutic program which strives to keep the environment and activities of the child as normal as possible.

Clay and Webster Streets.

CONGENITAL PNEUMONITIS IN NEWBORN INFANTS

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MINNEAPOLIS

THE EPIDEMIOLOGIC association of infection of the upper respiratory tract and primary atypical pneumonia has been reported from many sources.[1] Recently, serologic studies have demonstrated a direct causal relation between these diseases.[2] During the third epidemic of primary pneumonitis in Minnesota, which is reported elsewhere,[3] I observed for the first time babies ill with pneumonitis in the initial twenty-four hours of life. The mothers of several of these babies had evidence of infection of the upper respiratory tract at the time of delivery or shortly thereafter. This observation suggested that a common agent may be responsible for two seemingly different infections in which similar pathologic changes were observed. In the pharyngeal epithelium of both the mother and her baby there were many typical cytoplasmic inclusion bodies.

The frequent association of the common cold and atypical pneumonia is well known. An epidemiologic report by the Commission on Acute Respiratory Diseases[4] called attention to a definite, parallel rela-

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1. Reimann, H. A.: Acute Infection of Respiratory Tract with Atypical Pneumonia: Disease Entity Probably Caused by Filtrable Virus, J.A.M.A. **111**:2377 (Dec. 24) 1938. Iverson, H. A.: Epidemic of Acute Respiratory Disease Associated with Atypical Pneumonia, Bull. Johns Hopkins Hosp. **72**:89, 1943. Andrus, P. M.: Silent Bronchopneumonia, Canad. M. A. J. **47**:339, 1942. Becker, R. P.: Pneumonia Complicating Mild Respiratory Infections, ibid. **48**:324, 1943. Kennedy, J. A.: Pulmonary Complications of Common Cold and Sinusitis; Findings in Mass Radiography, Lancet **1**:769, 1943. Robertson, A. F., Jr.: Report of Epidemic of Acute Respiratory Infection with Pneumonitis, Virginia M. Monthly **69**:542, 1942. Favour, C. B.: Infections Associated with Epidemic of Primary Interstitial Pneumonia, New England J. Med. **230**:537, 1944. Breslow, L.: Epidemic of Acute Respiratory Disease Associated with Atypical Pneumonia, J. Clin. Investigation **24**:775, 1945.

2. Eaton, M. D., and Van Herick, W.: Serological and Epidemiological Studies on Primary Atypical Pneumonia and Related Acute Upper Respiratory Disease, Am. J. Hyg. **45**:82, 1947.

3. Adams, J. M.: A Third Epidemic of Primary Virus Pneumonitis Among Infants in Minnesota, Journal-Lancet **65**:192, 1945.

4. Epidemiology of Atypical Pneumonia and Acute Respiratory Disease at Fort Bragg, North Carolina, Commission on Acute Respiratory Diseases, Am. J. Pub. Health **34**:333, 1944.

tion between common diseases of the respiratory tract and atypical pneumonia. The authors of the report showed the reasonable constancy of a 10 to 1 ratio of patients admitted with infections of the respiratory tract to patients with atypical pneumonia, and they suggested the hypothesis that "atypical pneumonia may be a severe manifestation of the same specific infection or infections which produce common respiratory illnesses." MacLeod,[5] in the summary of his report on primary atypical pneumonia, stated in the final paragraph:

> The possibility exists that pulmonary involvement may occur in only a portion of the total number of individuals who suffer from the epidemic disease, and that the infection may be localized more commonly to the upper respiratory tract.

Eaton and Van Herick[2] performed virus neutralization tests on serums from 213 persons with various types of diseases of the respiratory tract. They observed significant increases of four fold or greater in titer of the serums of 52 of the 84 persons with primary atypical pneumonia and in 15 of the 77 with undifferentiated infections of the upper respiratory tract.

Dochez and his co-workers[6] successfully demonstrated that a filtrable agent is responsible for certain types of infectious colds. The Commission on Acute Respiratory Diseases[7] reported the experimental transmission of minor infections of the respiratory tract to human volunteers and concluded that at least two filtrable agents, presumably viruses, can induce these minor illnesses in man. Many other workers,[8] as well as the Commission on Acute Respiratory Diseases,[9] demonstrated the recovery of a viral agent from patients with atypical pneumonia. Most of these studies, except for the commission's report, were concerned with the sporadic infections. The present study demonstrates for the first time a possible pathologic association of primary pneumonitis of infancy with one of the mild infections of the upper respiratory tract.

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5. MacLeod, G. M.: Primary Atypical Pneumonia, M. Clin. North America **27**:670, 1943.

6. Dochez, A. R.; Shibley, G. S., and Mills, K. C.: Studies in Common Cold: Experimental Transmission of Common Cold to Anthropoid Apes and Human Beings by Means of Filtrable Agent, J. Exper. Med. **52**:701, 1930.

7. Commission on Respiratory Diseases, J. Clin. Investigation, to be published.

8. Weir, J. M., and Horsfall, F. L., Jr.: The Recovery from Patients with Acute Pneumonitis of a Virus Causing Pneumonia in the Mongoose, J. Exper. Med. **72**:595, 1940. Eaton, M. D.; Meiklejohn, G.; Van Herick, W., and Talbot, J. C.: Infectious Agent from Cases of Atypical Pneumonia, Apparently Transmissible to Cotton Rats, Science **96**:518 (Dec. 4) 1942. Horsfall, F. L., Jr.; Curnen, E. C.; Nirick, G. S.; Thomas, L., and Ziegler, J. E., Jr.: Virus Recovered from Patients with Primary Atypical Pneumonia, ibid. **97**:289, 1943.

9. Transmission of Primary Atypical Pneumonia to Human Volunteers, Commission on Acute Respiratory Diseases, J.A.M.A. **127**:146 (Jan. 20) 1945.

Primary virus pneumonitis, as previously reported,[10] is a disease of newborn and young infants, characterized by an acute onset of sneezing, coughing, dyspnea and cyanosis. Three distinct epidemics were observed; the incidence of infection in each was high. However, pneumonitis does not develop in all babies, some having minor symptoms of sneezing and coughing only. In the first two epidemics, 62 per cent of the patients had the characteristic symptom pattern of cough, dyspnea and cyanosis. The elevation in temperature was moderate to low, some infants showing no elevation. The mortality was definitely correlated with the severity of symptoms and signs. The mortality rate in the first two epidemics was 20 per cent.

The incidence of this disease according to age is significant, as it is confined almost entirely to the neonatal period. The oldest patient observed was an infant 32 weeks of age who was in a ward of infants with the disease. Prematurely born babies are very susceptible, and the mortality rate is extremely high among these patients.

The diagnosis is made from the symptom pattern and the rather characteristic shadows seen in the roentgenograms of the lungs. In addition, pharyngeal smears show epithelial cells in large numbers and an almost complete absence of bacteria and polymorphonuclear leukocytes. Many of the epithelial cells contain cytoplasmic inclusion bodies. When present in large numbers, they seem to have diagnostic significance.

Pathologic studies of sections of the lung of infants who have died of primary virus pneumonitis reveal a highly characteristic picture. As reported in detail in two previous papers,[10b, c] the prominent features are destruction and proliferation of bronchial epithelium, with peribronchial infiltration of mononuclear cells. Typical cytoplasmic inclusion bodies are present in the epithelial structures of the lungs and trachea. These bodies have all the characteristics of virus inclusions and are morphologically identical with the bodies seen in the passages of the upper respiratory tract in the acute stage of the disease. They are acidophilic with hematoxylin and eosin, and also with the Giesma stain. There appears to be a clear zone, or halo, about many of the inclusions. In sections of the lung their size varies from 3 to 6 microns in diameter. In pharyngeal tissues greater variation in size is seen, and granules occasionally occur in the body of the inclusion. However, single inclusions or inclusions at either end of the nucleus are considered

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10. *(a)* Adams, J. M.: New Form of Virus Pneumonitis Occurring Epidemically Among Newborn Infants, Proc. Soc. Exper. Biol. & Med. **46**:114, 1941; *(b)* Primary Virus Pneumonitis with Cytoplasmic Inclusion Bodies: A Study of Epidemic Involving Thirty-Two Infants, with Nine Deaths, J.A.M.A. **116**:925 (March 8) 1941. *(c)* Adams, J. M.; Green, R. G.; Evans, C. A., and Beach, N.: Primary Virus Pneumonitis: Comparative Study of Two Epidemics, J. Pediat. **20**:405, 1942.

the most significant. Figure 1 shows what are considered significant inclusions from the pharynx and the lung. For further details of the pathologic changes, the previous publications may be consulted. The

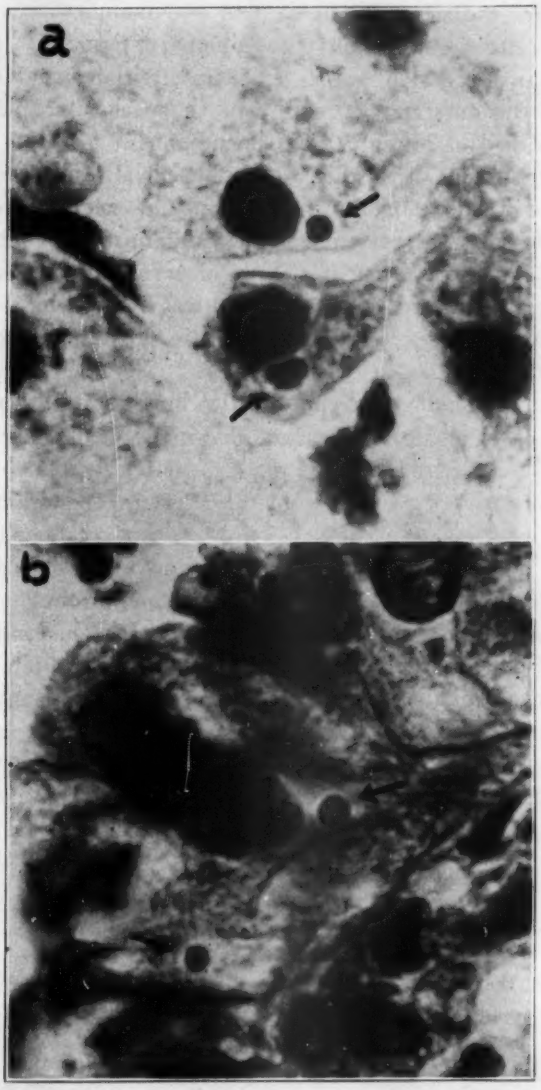

Fig. 1.—*(a)* Typical cytoplasmic inclusions in the pharyngeal epithelium; *(b)* inclusion bodies in the epithelium of the lung shown for comparison. The sections were stained with hematoxylin and eosin.

pathologic picture in the affected infants is identical with that reported by most authors for atypical pneumonia, except for the pres-

ence of cytoplasmic inclusion bodies. Golden,[11] reporting from the Institute of Pathology of the Army Medical Museum on patients with "atypical pneumonia, etiology undetermined," cited considerable evidence for the viral nature of this infection, the close similarity to acute influenzal and measles pneumonia and the inability to demonstrate consistently any organisms in the pulmonary tissue. He further emphasized that the lesion is an acute interstitial pneumonitis. This change was the outstanding feature of the pathologic picture in the infants who died of primary virus pneumonitis.

In the treatment of this disease, no beneficial results were obtained from the use of sulfonamide drugs or penicillin except when secondary bacterial infection was present. Oxygen, administered continuously, is of great benefit. More recently, the use of normal human serum U.S.P. and concentrated human gamma globulin was found helpful in moderating the disease picture. If given early, these substances probably have a prophylactic effect.

The third epidemic of pneumonitis to be observed by me made its appearance early in March 1945 and continued until the latter part of April. On March 25, smears were made of material from the pharynges of 12 mothers who were in the obstetric service and were studied for the presence of inclusion bodies. Nine of the specimens yielded no organisms. The smear from Mrs. B., whose baby had pneumonitis, showed many inclusion bodies (case 1). The smear from another mother was slightly positive for inclusion bodies, but she had no symptoms. Mrs. F. had not been delivered, but she had acute nasopharyngitis and said she had a "cold." Her pharyngeal smear showed many typical inclusion bodies, 6 to 10 positive cells per hundred cells counted. She was delivered on March 31, and her baby had a smear showing the inclusion bodies six hours after delivery. This case is the second of those to be reported, illustrating the congenital occurrence of the disease.

REPORT OF CASES

CASE 1.—Baby B., a boy, was born on March 19; weight at birth was 2,725 Gm. His condition was fair for the first twenty-four hours, at which time cyanosis of the hands and feet, the presence of excessive mucus and vomiting were recorded. He was given 25 cc. of normal human serum U.S.P. subcutaneously and was isolated with his mother in her room. The second day after birth the respirations became rapid and continued so for the next few days. The baby nursed poorly. On March 23, the fourth day of life, smears of material from the pharynx were strongly positive for inclusion bodies. A roentgenogram of the chest showed a distinct increase in the bronchovascular markings on both lungs, and the baby was transferred to the isolation unit of the pediatric service with a diagnosis of pneumonitis. A smear of material from the mother's pharynx taken on March 25 revealed many typical inclusions in the pharyngeal epi-

11. Golden, A.: Pathologic Anatomy of "Atypical Pneumonia, Etiology Undetermined"; Acute Interstitial Pneumonitis, Arch. Path. **38**:187 (Oct.) 1944.

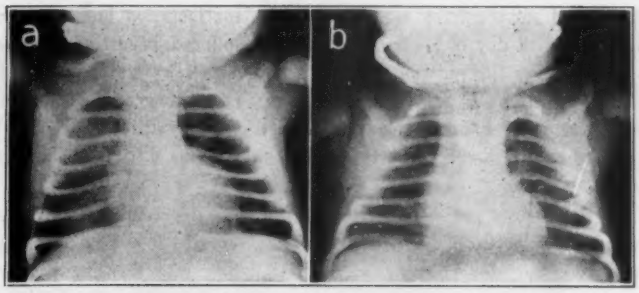

Fig. 2.—Lungs of baby W. (case 3). The roentgenogram in *a* was taken twenty-four hours after birth and shows a soft shadow in the upper and lower lobes of the right lung on the right side, and that in *b* was taken one week later.

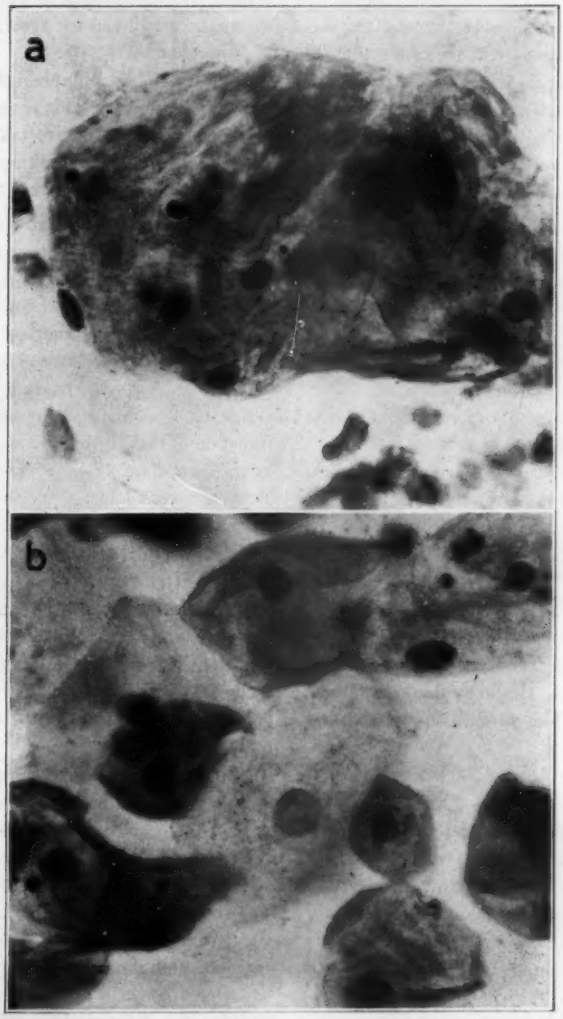

Fig. 3.—Photomicrographs of the pharyngeal epithelium *(a)* of baby W. (case 3) and *(b)* of Mrs. W., showing the cytoplasmic inclusion bodies. The smears were made twenty-four hours after delivery. Hematoxylin and eosin stain.

thelium. A smear from the baby was also positive for inclusion bodies on this date. On March 24, the fifth day of life, cyanosis was pronounced, occurring in attacks, and rales were present over the pulmonary fields. Oxygen therapy was given continuously until March 29. On March 26 the infant was given 2 cc. of concentrated human gamma globulin intramuscularly. Except for one spike in the temperature to 103.4 F. (rectal), the course of the baby's illness was afebrile. The patient was discharged in good condition on April 3.

CASE 2.—Baby F., a girl, was born on March 31; the weight at birth was 3,765 Gm. Examination on her admission to the nursery revealed a normal newborn infant. During the first twenty-four hours, occasional coughing and sneezing were recorded. On April 1, the temperature reached 100 F. (rectal), and again on April 4 it was 100.8 F. (rectal). Concentrated human gamma globulin, 2 cc., was given intramuscularly on the day of birth and again on the second and the ninth days after birth. Coughing with slight cyanosis was recorded on April 3; an increased amount of mucus was also noted. The mild cough, the sneezing and the increased mucus continued for several days, but the course of the patient's illness remained mild throughout.

On March 25, five days before delivery, the mother had complained of a fresh cold, slight cough and a thin, watery discharge from her nose. A pharyngeal smear on that date revealed many inclusion bodies in the epithelial cells. Smears taken again on the day of delivery were strongly positive for the bodies. The infant's pharyngeal smear was positive six hours after birth and strongly positive on the fifth day of life.

CASE 3.—Baby W., a boy, was born on April 9, 1945; his weight at birth was 3,170 Gm. The initial examination revealed a normal, healthy-appearing newborn infant. He was reexamined on April 10 because of coughing, sneezing, nasal discharge and copious pharyngeal mucus. The respiratory rate was 83 per minute and the temperature 98.6 F. (rectal). The lungs showed occasional moist rales. Oxygen therapy was started after the respiratory rate had risen to 92 per minute. After oxygen was administered, the rate fell to 62 per minute, and the color was better. A roentgenogram of the chest taken twenty-four hours after birth showed definite changes in the right lung; a diffuse process and some consolidation in both the upper and the lower lobe were reported. A week later decided clearing of the process in the lung had occurred. The two roentgenograms are shown in figure 2. A definite history of recent infection of the respiratory tract in the mother of this infant could not be obtained. Pharyngeal smears from the mother and the baby twenty-four hours after delivery showed many typical inclusion bodies. These bodies are shown in figure 3. Subsequent smears from both the mother and her baby were also strongly positive. Further laboratory data were without significance. Concentrated human gamma globulin, 2 cc., was given intramuscularly two hours after birth and again on the fourth day of life. The course of the infant's illness was uneventful, although the respiratory rate continued to be irregular and rapid for several days. The patient was discharged in good condition on the tenth day with his mother.

CASE 4.—Baby S., a boy, was delivered on March 15, 1945, by cesarean section; the weight at birth was 3,850 Gm. During the first day, sneezing, with the presence of some excess mucus in the throat, was noted. The hands and feet were cyanotic. On March 16, coughing, with vomiting of mucus, was noticed. Respirations were noisy, and further sneezing and coughing were recorded by the nurse. The mucus was again excessive, and a dusky color was evident. A gavage tube was passed to check the patency of the esophagus. Again, on March 17, sneezing and coughing of mucus were still present. On March 19, concentrated human gamma globulin, 2 cc., was given intramuscularly.

Pharyngeal smears made fifteen minutes after the delivery by cesarean section showed cytoplasmic inclusion bodies (fig. 4). The mother's pharyngeal exudate was

checked on March 17 and found to be strongly positive for inclusion bodies. A diagnosis of pneumonitis in this patient was not established, but the baby had a definite infection of the upper respiratory tract. Concentrated human gamma globulin may have played a role in modifying his illness.

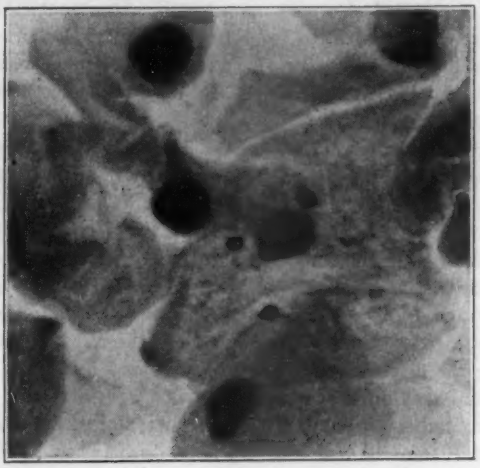

Fig. 4.—Photomicrograph of the pharyngeal epithelium of baby S. (case 4) prepared fifteen minutes after delivery by cesarean section. It shows three cytoplasmic inclusion bodies in one cell. Hematoxylin and eosin stain.

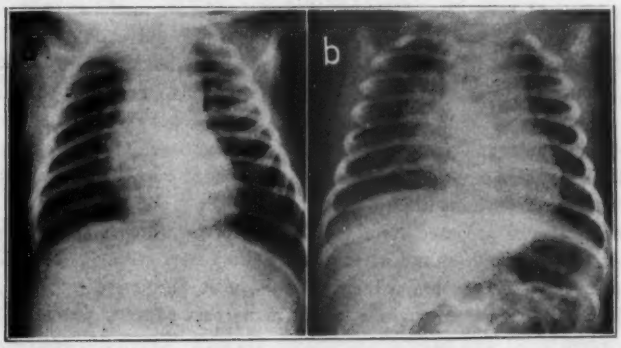

Fig. 5.—Lungs of baby P. (case 5). The roentgenogram in *a* shows diffuse, soft shadows with slight infiltration in the base of the right lung, and that in *b* shows some increase in the process, with abnormal shadows on the right side, involving the upper and lower lobes.

The following patients were observed in September and October 1945, and their cases are included because they seem to be excellent examples of congenital pneumonitis.

CASE 5.—Baby P., a girl, was born on Sept. 4, 1945; her weight at birth was 3,650 Gm. During the first twenty-four hours the patient appeared normal, except for slight cyanosis of the hands and feet. On September 5, however, an increased respiratory rate and generalized cyanosis were noted. The temperature reached 100.6 F. (rectal) and remained elevated for two days. A roentgenogram of the chest on September 6 showed irregular aeration of the lungs, with increase in the markings and slight infiltration of the base of the right lung. The heart was not enlarged. Sneezing and coughing were

first noticed on September 7. The patient continued to have cyanotic attacks, which became severe on September 11, and a roentgenogram at this time showed an increase in the process, with a larger soft shadow on the right side involving the upper and lower lobes. Two of the patient's roentgenograms are shown in figure 5. On examination rales were heard over both pulmonary fields posteriorly.

The mother complained of a sore, scratchy throat on September 7, and on that day her temperature was elevated to 101 F. (rectal). There was an increase in exudate in her throat, which was mildly infected. Smears taken showed many cytoplasmic inclusion bodies in the epithelial cells. There were many sloughing cells on the slide and a few bacteria and leukocytes.

The smear from the baby's throat showed only epithelial cells, which were heavily filled with inclusion bodies. Several subsequent smears from the mother and the baby remained strongly positive.

The father, who was a senior medical student, had a typical cold during the week preceding the delivery of the patient.

Normal human serum U.S.P., 20 cc., was given subcutaneously to the baby on September 12, 14 and 16. The patient's temperature returned to normal on the third day and remained there. Cyanosis persisted in a mild degree. Oxygen therapy was used irregularly during the first week of life. The patient was discharged on September 29, with no further clinical evidence of pneumonitis.

CASE 6.—The father of Baby W., a girl, first noticed symptoms of a cold on October 16, at which time he had a cough, nasal discharge and persistent hoarseness. The mother and father were associated until the mother's admission to the hospital on October 22. Thirty-six to forty hours after delivery, she noticed cough and a nasal discharge, as well as hoarseness and a "tickle" in her throat. She had not seen her baby at this time and was isolated. Her temperature was 101.4 F.

The patient had been delivered without event and sent to the nursery. Mucus in the throat was troublesome the first twenty-four hours and caused one episode of cyanosis. Between thirty-six and forty hours after birth, coughing, sneezing and occasional choking were noticed. Some cyanosis was present. At sixty-eight hours, sneezing, coughing and profuse nasal discharge were evident. The baby was transferred to the pediatric isolation unit, and a roentgenogram of the chest was taken. The film showed "a minimal degree of increase in the marking throughout both lungs, which would be consistent with early pneumonitis."

Pharyngeal smears prepared from the patient forty-six hours after delivery were slightly positive for inclusions, and at sixty hours they were strongly positive (20 cells per hundred counted cells contained inclusion bodies). Smears of material from the mother's pharynx were strongly positive sixty hours post partum, showing 22 positive cells per hundred cells. The patient's symptoms gradually improved, and she was discharged on the eleventh day with her mother. The course in the hospital was afebrile.

COMMENT

Knowledge of primary pneumonitis is adequate to substantiate the diagnosis from the clinical, epidemiologic and pathologic points of view. In addition, washings from the throats of infants ill with this disease have produced diseases of the respiratory tract in newly born calves, and, on the fourth day after nasal inoculation, smears of the material from the calves' respiratory passages have shown typical inclusion bodies.[12] We have not as yet attempted neutralization of the disease in

12. From unpublished preliminary data obtained in cooperative studies with Dr. Roepke and Dr. Malmquist of the University of Minnesota, Department of Veterinary Medicine.

the calf. Evidence has been presented which suggests that normal human serum U.S.P. or concentrated gamma globulin of human source has some of the necessary factors for amelioration and possible prevention of primary pneumonitis of infancy.

Previously, attention was called to the fact that the prematurely born baby is highly susceptible to this disease. Additional experimental and clinical evidence in the literature suggests that immunity is transferred to the baby during the latter part of its intrauterine life. The full term newborn infant in the main may be partially immune as compared with the prematurely born baby. Older children and adults probably manifest this same immunologic difference. In the first and second epidemics referred to,[10c] the peak of the attack affected babies in the fourth week of life, suggesting a rapid loss of neonatal immunity. This concept of immunity seems to be strengthened by the material presented in this paper, which suggests the same agent as the cause of the pneumonitis of infancy and of a mild infection of the respiratory tract in the mother. The common cold is recognized as a mild disease of the upper respiratory tract in its pure form in the regions of the world where it is prevalent. Partial immunity in the human host may be responsible for this occurrence. The Commission on Acute Respiratory Diseases recently showed that immunity exists in man to one of the types of mild disease of the respiratory tract which they studied. Our recent report on a clinical trial of gamma globulin in the prevention of common diseases of the respiratory tract furnished further evidence on this point.[13]

The significance of inclusion bodies in many virus diseases has been well established. Their presence in pathologic material deep in the lung structure of infants who die of this pulmonary disease is a fact. The occurrence of the bodies in large numbers in the passages of the upper respiratory tract of these infants, in contrast to their absence in controls, is also a constant observation. As pointed out previously, the morphologic and staining characteristics of the bodies seen in the upper and in the lower respiratory tract are identical.

There are undoubtedly many unknown viruses which affect the respiratory passages. The known viruses include Hemophilus influenzae A and B, the measles virus, the Dochez common cold virus, the atypical pneumonia virus isolated by the Commission on Acute Respiratory Diseases and a few others isolated by workers in sporadic cases of atypical pneumonia. The commission also isolated two agents from mild diseases of the respiratory tract which appear to be viral in nature. The psittacosis group of viruses and the agent of lymphocytic chorio-

13. Adams, J. M., and Smith, N.: Clinical Trial of Gamma Globulin in the Prevention of Common Respiratory Diseases, Proc. Soc. Exper. Biol. & Med. **63**:426, 1946.

meningitis should be included with known viruses. Golden[11] did not describe inclusion bodies in the pathologic material of "atypical pneumonia, etiology undetermined." Pinkerton, Smiley and Anderson[14] described cytoplasmic and intranuclear inclusions in the pulmonary tissue of 5 patients with Hecht's giant cell pneumonia. Goodpasture and his co-workers[15] recorded intranuclear inclusions in persons with secondary virus pneumonia. In variola and vaccinia pneumonias[16] cytoplasmic inclusion bodies resembling Guarnieri bodies were often present in the bronchial epithelium. In a study of an epidemic occurring in 1937, I reported the constant occurrence of typical cytoplasmic inclusion bodies in the alveolar, bronchiolar and bronchial epithelium of the lungs of patients who died of primary "virus" pneumonitis of infancy.

In this communication, it is suggested that primary pneumonitis of infancy may be caused by the same agent that is responsible for at least one of the mild infections of the upper respiratory tract in older children and adults. Clinical, pathologic and some immunologic, as well as preliminary experimental, evidence has been presented to substantiate this causal relation.

SUMMARY

A relation between infections of the upper respiratory tract in mothers and primary pneumonitis in their infants is likely. It is suggested that the same causative agent may be involved and that this agent may be responsible for pathologic changes in the pharyngeal epithelial cells of both the mother and her baby. These changes are represented by large numbers of typical cytoplasmic inclusion bodies seen in the pharyngeal epithelium of both the mother and the baby and in the alveolar and bronchial epithelium of the infants who die of pneumonitis. A similar causal relation, both epidemiologic and serologic, of diseases of the upper respiratory tract to atypical pneumonia is suggested in several reports now in the literature.

Reports of 6 cases of congenital infections of the respiratory tract constitute the major subject of this paper. A brief review of the pertinent features of primary virus pneumonitis is presented, with therapeutic suggestions. Normal human serum U.S.P. and concentrated human gamma globulin appear to be beneficial, particularly when given early in the course of the disease.

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14. Pinkerton, H.; Smiley, W. L., and Anderson, W. A. D.: Giant Cell Pneumonia with Inclusions: Lesions Common to Hecht's Disease, Distemper and Measles, Am. J. Path. **21**:1, 1945.

15. Goodpasture, E. W.; Auerbach, S. H.; Swanson, H. S., and Cotter, E. F.: Virus Pneumonia of Infants Secondary to Epidemic Infections, Am. J. Dis. Child. **57**:997 (May) 1939.

16. Reimann, H. A.: The Viral Pneumonias and Pneumonias of Probable Viral Origin, Medicine **26**:167, 1947.

TUBERCULOSIS IN CHILDREN

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DESPITE THE FACT that children not uncommonly have other forms of tuberculosis, most previous articles have been confined to the study of the primary complex. It is my purpose to enumerate the diversity of paths over which the disease may travel within the youthful host and to fix attention on the protean character of tuberculosis in the young child.

This study was based on 90 cases of tuberculosis in children who were seen at autopsy at Sea View Hospital. Only children who had not reached their thirteenth birthday were included in the study. If older children were chosen, there might be a question as to whether they should not be included in the adolescent group.

Age.—From the table, it may be seen that 40 per cent of all the patients were observed in the first three years of life. This span represents the age period in which the primary complex develops most frequently.

Race.—In this series there were 61 (67.8 per cent) Negro children and 29 (32.2 per cent) white children. From a review of 1,000 autopsy reports on tuberculous patients of all ages from the same institution, it was seen that 61.3 per cent of patients were white and 37.7 per cent were Negro. A study of this general series revealed that the proportion of Negro to white persons decreased with each succeeding decade. Among 20 patients over 70 years of age, there was only 1 Negro.

A number of factors may explain the preponderance of Negro children in this group. The large number of deaths in the first three years of life is the result of the progressive primary complex, a condition occurring predominantly in the Negro.[1] In addition, in the Negro there is a tendency for a large primary complex to develop. The complex is an indication either of an overwhelming infection or of poor resistance to the invading organisms on the part of the host. I am not prepared to say whether either or both of these factors contributes to the development of a large primary focus. The larger the focus, the greater the possibility of sequelae developing from it. I believe there is ample proof

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1. Auerbach, O.: The Progressive Primary Complex, Am. Rev. Tuberc. 37:346-353 (March) 1938.

that after the development of the primary focus lymphatic dissemination does not halt at the regional lymph nodes but continues into the venous blood stream. The larger the primary focus, the larger and more numerous will be the hematogenous seedings. The greater frequency of skeletal tuberculosis and of tuberculomas of the brain in the Negro can be explained on this basis.

Sex.—There were 43 (47.8 per cent) girls and 47 (52.2 per cent) boys in this series. This proportion is in contrast to that in the general autopsy series, of which 28.5 per cent were female and 71.5 per cent male patients. With increasing age, the number of deaths in male patients rose sharply.

Pathologic Changes.—Tuberculous processes in the child fall into two categories: (1) those in which the pathologic processes are directly or indirectly the result of the primary complex, and (2) those in which

Distribution of the Ninety Children in the Series by Age, Race and Sex.

	Months				Years									
	2½ to 11	1 to 2	2 to 3	3 to 4	4 to 5	5 to 6	6 to 7	7 to 8	8 to 9	9 to 10	10 to 11	11 to 12
No. of children	7	19	10	5	4	1	3	7	8	2	5	7
	Race									Sex		
	Negro Children 62 (68.9%)			White Children 28 (31.1%)				Boys 43 (47.8%)				Girls 47 (52.2%)

a new tuberculous process develops, independent of the primary complex. Whereas in adults the latter condition occurs far more frequently, among children the first group of processes predominates.

Pulmonary Pathologic Changes.—Three types of lesions were observed in children: the primary complex, hematogenous tuberculosis and chronic pulmonary tuberculosis.

THE PRIMARY COMPLEX

In the vast majority of cases the primary complex goes on to anatomic healing; but in a small number it may continue to progress.

Healed or Healing Primary Complex.—The pathologic anatomy of the healing primary focus was amply described by Ghon,[2] Kuess[3] and Blacklock.[4] Lesions of this type were observed in 66 of the patients in this series, the youngest of whom was 18 months of age. In 15 older children, the lungs showed no other pathologic changes, although concurrent extrapulmonary tuberculosis did exist.

2. Ghon, A.: Der primaere Lungenherd bei der Tuberkulose der Kinder, Berlin, Urban & Schwarzenberg, 1912.

3. Kuess, G.: De l'heredite parasitaire de la tuberculose humaine, Paris, Asselin & Houzeau, 1898; cited by Ghon.[2]

4. Blacklock, J. W. S.: Tuberculous Disease in Children: Its Pathology and Bacteriology, Medical Research Council, Special Report Series, no. 172, London, His Majesty's Stationery Office, 1932.

In 3 children the primary focus, which had undergone liquefaction with formation of a cavity, contained calcified particles. The wall of the cavity had become hyalinized or showed far advanced healing, and the regional lymph nodes showed a caseous, calcified central zone surrounded with a layer of hyalinized connective tissue. All 3 children were Negro, and their ages were 15, 18 and 24 months, respectively. Two interesting questions present themselves: 1. Should a condition such as that of these children be classified as a progressive primary complex? 2. To what extent may a primary focus progress and still undergo anatomic healing?

In answer to the first question, in these children, undoubtedly, there was a progression of the primary focus, even to the point of liquefaction, but the course was then reversed toward anatomic healing. Since in all 3 children the regional lymph nodes showed healing changes in advance of the primary focus, it is my impression that the blocking of the process at this point prevented further progression and was a factor in the healing of the advancing primary complex.

In answer to the second question, it may be pointed out that in these children the size of the excavations was the same as that of many progressive primary foci.

There were 19 children who showed, in addition to the healing primary focus, a miliary dissemination in the lungs and in other parenchymatous organs, such as the liver, spleen and kidneys.

Progressive Primary Complex.—The progressive primary complex was present in 23 of the patients of this series. The youngest child was 8 months and the oldest 9 years of age. In a previous study[1] of this disease pattern, I observed that all but 1 of 17 children were Negro. In this group only 4 of 23 children were white. There can be no question that the progressive primary complex occurs chiefly in Negro children.

Children with this form of the disease exhibit a progressive enlargement of the primary focus and of its lymph node components. Tendency to encapsulation is slight, and the predilection to liquefaction and formation of a cavity is strong. The latter process was observed in 10 of the 23 children. The primary focus is of the same size as, or may be even larger than, the much enlarged regional lymph nodes. This enlargement does not usually occur when the primary focus goes on to healing. Calcification was absent in all 23 children.

In the more advanced cases the primary focus may progress to involve the greater part of a lobe, liquefaction often accompanying this extension. The evacuation of the liquefied material results in an irregular, shaggy excavation. The wall of the cavity is not well defined, and large caseous masses form the inner wall and represent incomplete liquefaction. Trabeculae, which are almost constantly present in cavities

of chronic pulmonary tuberculosis, are usually absent from these excavations.

Involvement of the lymph nodes in the progressive primary complex is extensive and advanced. Lymph nodes as far afield as the cervical and peripancreatic groups are often involved. Although caseation does occur in the lymph nodes of the opposite side, the most complete involvement is encountered in the nodes on the side of the focus. The lymph nodes from the focus to the tracheobronchial angle are considerably enlarged and completely caseous; frequently they have undergone central liquefaction. They are matted together and often cause

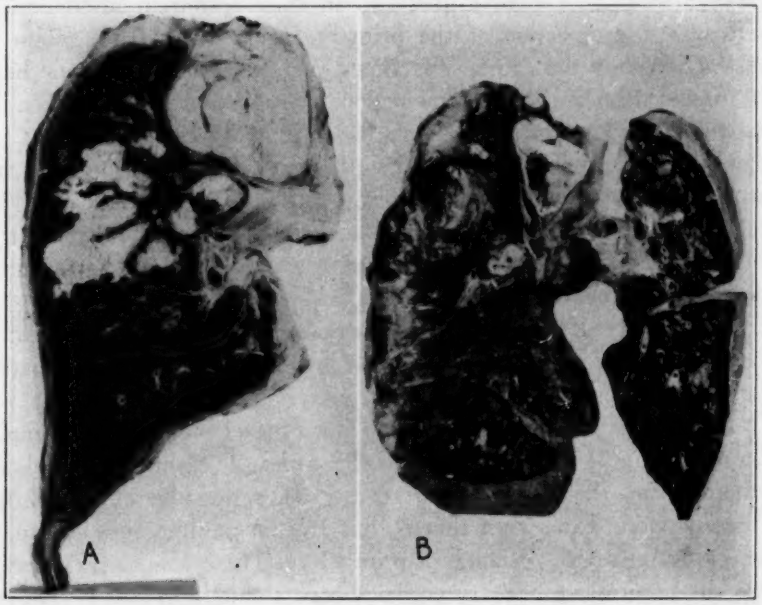

Fig. 1.—*A*, progressive primary complex in a 4 year old Negro boy. The enlarged primary focus occupies more than half the upper lobe of the right lung. The caseous peribronchial and tracheobronchial nodes are in the same stage of anatomic development. A caseous pleuritis is also present. *B*, progressive primary complex in a 9 month old Negro boy. The primary focus in the upper lobe of the right lung and the corresponding right superior tracheobronchial lymph nodes are in the stage of liquefaction. The caseous foci in both lungs are due partly to a bronchogenic dissemination and partly to a hematogenous dissemination.

pressure on the surrounding structures, such as the trachea, the bronchi and the blood vessels. The enlarged inferior tracheobronchial nodes cause a wide seperation of the bronchi. In 2 children in this series a liquefied focus ruptured into a bronchus.

HEMATOGENOUS TUBERCULOSIS

The hematogenous dissemination which develops in children may occur in one of two ways: as the result of a dissemination into the blood stream after the development of a primary complex (early generaliza-

tion) or as the result of a hematogenous dissemination from an active extrapulmonary tuberculous process after the primary complex has healed (late generalization).

Early Generalization.—Two types of hematogenous dissemination occur from the fresh primary complex: early abortive generalization and early progressive generalization.

Early Abortive Generalization: It has been my opinion for some time that in every instance in which a primary complex develops in the lungs there is a hematogenous dissemination to the various organs. The disseminations cease and the miliary foci undergo anatomic healing as soon as the primary complex is sealed off by encapsulation. That there is more than one seeding is evidenced by the different anatomic ages of the miliary foci. Generally, the size and number of the hematogenous seedings depend on the extent of the primary complex. When there is a small primary complex, the hematogenous foci are small and not numerous.

The hematogenous disseminations usually occur in the parenchymatous organs and in the lungs, in which they have a characteristic distribution. The foci in the pulmonary parenchyma are larger and more numerous in the apical and ventral aspects of the lungs.

The healing and gradual disappearance of these foci can be followed roentgenographically. The effacement of the foci proceeds from base to apex. In a previous study I described this process.[5] As they undergo anatomic healing, miliary tubercles composed of epithelioid and giant cells are gradually replaced with collagenous connective tissue. The hyalinized foci, which are round or oval at the beginning, are thinned and stretched by the surrounding parenchyma of the lung to which they are attached. Recognition of the tuberculous origin of these thinned areas of connective tissue is no longer possible, since they contain no epithelioid or giant cells. As they heal and shrink, the foci stretch and tear the surrounding alveolar septums. The smaller nodules are the first to be replaced with connective tissue, while the larger foci in the apical portions of the lungs are the last to be so affected. Some of the apical nodules may be larger than miliary tubercles, and they frequently contain a caseous center. In some instances, if it is large enough, the caseous center may become encapsulated, instead of being replaced with fibrous tissue.

An erroneous impression would be derived from an examination of lungs containing hematogenous foci at intermediate stages of anatomic healing. In stages of far advanced healing, the number of miliary foci is only moderate, and they are usually seen in the upper pulmonary fields. Still later the foci might be present only in the apical portions of

5. Auerbach, O.: Acute Generalized Miliary Tuberculosis, Am. J. Path. **20**:121-136 (Jan.) 1944.

the pulmonary fields. One might consider that the hematogenous dissemination occurring from the primary complex was limited to the upper pulmonary fields. Proof that the hematogenous infection originally involved all lobes of the lungs is seen in serial roentgenographic studies of these patients who had early generalization of the disease. Roentgenograms of the chest at first show a diffuse hematogenous distribution. In subsequent roentgenograms, there is a gradual clearing of the shadows in a caudal-cephalic direction. Autopsies on patients in whom the process was in the clearing phase showed healing miliary foci still present in the parenchyma of the lung, although on roentgenographic examination they had disappeared. These shrunken foci, which microscopically are composed of hyalinized connective tissue with occasional epithelioid and giant cells, are surrounded with a wide zone of emphysema which camouflages their presence.

That this dissemination may clear completely in a short time is demonstrated by 1 of my patients. A 22 month old girl who died of tuberculous peritonitis secondary to caseous salpingitis showed an encapsulated caseous calcified primary complex and clear pulmonary fields. That a generalized hematogenous dissemination had occurred from the primary complex was seen in the presence of miliary tubercles in the stage of far advanced healing within the spleen and liver.

In the great majority of cases, the primary complex and the early, abortive hematogenous seedings heal with no further tuberculous activity. The only anatomic change is a calcified or ossified primary complex. Less frequently, apical foci of miliary size (Neumann foci) or the larger, caseous and calcified (Simon foci and Aschoff-Puhl foci) are seen. Careful study of the liver and spleen at routine autopsies has revealed a fair number of caseous, calcified foci as remnants of this dissemination.

Although most of these hematogenous foci heal, in a small number of cases the tuberculous process progresses in one or, rarely, two organs. These organs, in order of frequency, are usually the skeletal system, the cerebral parenchyma, the fallopian tubes, the kidneys and the male genital system.

With the development of an active tuberculous process in one of these organs, the three stages of the Ranke classification are then present in 1 person. In these cases the tuberculosis of the isolated organ stems from the primary complex.

In some of these cases the tuberculous process developing from the hematogenous seeding leads to death, while the other foci of the early abortive generalization are undergoing anatomic healing. This condition is observed chiefly in cases in which the patients die of tuberculous meningitis, following the rupture of a tuberculoma of the brain, or of tuberculous peritonitis secondary to tuberculous salpingitis.

In other cases, the tuberculosis of the isolated organ, particularly skeletal tuberculosis, continues over a number of years, and the only remnants of the early abortive generalization are the apical foci and the occasional caseous, calcified foci encountered in the liver and spleen.

Early Progressive Generalization: In contrast to the early abortive generalization is the early progressive generalization. In these cases the source of the bacillemia, instead of becoming walled off, undergoes progression (progressive primary complex). As a result, hematogenous disseminations continue until death intervenes.

All 23 children with progressive primary complex in this series showed evidence of hematogenous dissemination. In addition to miliary foci, most of the children showed larger caseous foci, usually measuring up to 1 cm. in diameter. The presence of large caseous foci and the great variation in the size of these foci are in contrast to the hematogenous dissemination occurring in the early abortive seedings and the hematogenous dissemination secondary to extrapulmonary tuberculosis. Large nodular seedings, although most prominently seen in the lungs and spleen, are also observed in the liver, kidneys, adrenal glands and, less frequently, in the brain.

After the primary focus has undergone liquefaction, with resulting bronchogenic spread, it is impossible to distinguish these foci from those which occur as a result of hematogenous dissemination. In both instances the end product is a lobular caseous pneumonia, which has little tendency toward encapsulation.

Late Generalization.—In 6 children in this series the acute generalized miliary tuberculosis was secondary to an active extrapulmonary tuberculous process. The tubercle bacilli which were drained into the regional lymph nodes emptied into the venous circulation, whence they were carried into the various parenchymatous organs. The ages of these children varied from 7 to 11 years. In all cases the primary complex was well encapsulated, with calcium in its center. The miliary tubercles were of a more recent origin than the active extrapulmonary tuberculous process. The gross and microscopic pictures were those of acute generalized miliary tuberculosis, entirely similar to that seen in adults.

CHRONIC PULMONARY TUBERCULOSIS

There were 20 children with chronic pulmonary tuberculosis in this series. A healed primary complex in the lungs was evident in every child, so that it could not be thought that chronic lesions were primary foci. This high incidence of chronic pulmonary tuberculosis in children is surprising, since it has been generally accepted that the condition is almost exclusively limited to adults. Indeed, the term "childhood tuberculosis" has been used to distinguish tuberculosis in children from that in adults.

The youngest child with chronic pulmonary tuberculosis was 18 months of age; another child was 4 years old, and the other 18 children were from 7 to 12 years of age. Eight children (40 per cent) were white, while 12 (60 per cent) were Negro.

In every child in this group the primary complex had undergone anatomic healing, as evidenced by calcification and encapsulation. This healing, I believe, is ample proof of the assumption that the chronic pulmonary tuberculosis did not develop from the primary complex. In several of these children encapsulated, calcified foci were observed in the liver and spleen, an indication of healed early hematogenous dissemination occurring from the primary complex.

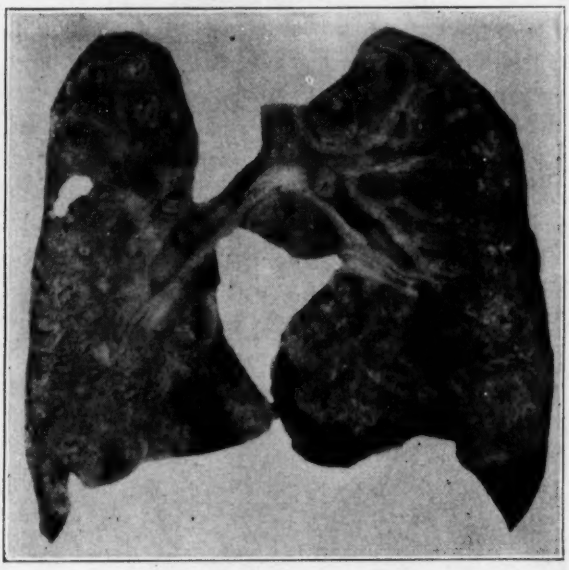

Fig. 2.—Chronic pulmonary tuberculosis in a 4 year old Negro child. In addition to the cavities, there are large acinous foci in the lower lobes.

The clinical course and the roentgenographic picture were entirely similar to those of chronic pulmonary tuberculosis in adults. The illness was usually ushered in with cough, expectoration and pain in the chest. The duration of the illness varied from four to thirty-three months. In 1 child artificial pneumothorax was maintained for six months, while in another a lobectomy was performed. In all but 1 child, who was 18 months of age, the sputum and/or gastric lavages yielded tubercle bacilli. It is of incidental interest that 4 of the children in this group had congenital heart disease, in the form of the tetralogy of Fallot.

The observations at autopsy on these children were almost entirely similar to those in chronic pulmonary tuberculosis in adults. The older cavities are situated in the upper portion of the upper lobes of the

lungs, and have much thicker and more fibrous walls than those seen in a progressive primary complex which has undergone liquefaction. Foci resulting from bronchogenic dissemination show a much less fulminating character than those resulting from liquefied primary foci. Indeed, the bronchogenic seeding in this older type of disease usually takes the form of acinous foci, and such caseous lobular pneumonia as does occur usually becomes encapsulated.

There is one important difference between chronic pulmonary tuberculosis in adults and the disease in children, a difference which I have noted in the adolescent also. Whereas in my autopsies on adults with chronic pulmonary tuberculosis gross caseation of the tracheobronchial lymph nodes was infrequently observed, the lymph nodes in this group of children were caseous in 7 instances (35 per cent).

SKELETAL TUBERCULOSIS

In 21 (23.3 per cent) of the 90 children active tuberculosis of the bone was present. This incidence compares with that of 10.1 per cent in a group I previously reported on, which included persons of all ages. Both Wullstein[6] and Cheyne[7] stressed the preponderance of tuberculosis of the bone in the younger age groups.

Age.—The youngest child in this series was 18 months of age; 2 were 2 years old; 3 were 3 years old, and the ages of the remaining 15 varied from 5 to 12 years.

Sex.—Thirteen of the 21 patients were boys and 8 were girls. In my previous report on skeletal tuberculosis in patients of all ages more than 70 per cent of the patients were men. This similarity is even more striking because in this present series the majority of deaths were among girls (52 per cent), while in the general autopsy series deaths among males predominated. I am unable to explain the preponderance of skeletal tuberculosis in men.

Distribution.—Thirteen of the 21 patients had tuberculosis of the spine; 7, tuberculosis of the hip joint; 2 each, tuberculosis of ribs and skull, and 1 each, tuberculosis of the ankle joint, the wrist joint, sacroiliac joints and the humerus. In 15 patients the tuberculous process was present in only one portion of the skeletal system; in 5 patients two parts were affected, and in 1 three sites were involved.

Pathogenesis.—It is generally agreed that tuberculous infection of the skeletal system occurs by way of the blood stream. In this series there was little doubt that the hematogenous dissemination had its origin in the primary complex. Only 1 patient in this series, an 8 year

6. Wullstein, L.: Spondylitis and Spondylarthritis tuberculosa, in von Joachimsthal: Handbuch der orthopaedischen Chirurgie, Jena, Gustav Fischer, 1905-1907.

7. Cheyne, W. W.: Pathology of Tuberculous Diseases of Bones and Joints, Brit. M. J. **1**:738-743 (April 4) 1891.

old girl, had chronic pulmonary tuberculosis. This condition was of recent origin and had developed many years after the onset of the skeletal tuberculosis. In 3 other children the urogenital system was concomitantly involved, but the involvement was of a more recent origin than the skeletal tuberculosis. In the other 17 patients, the skeletal involvement was associated with a primary complex. Nine of these children also had foci of the early generalization.

The question arises why skeletal tuberculosis does not occur more frequently from early abortive generalization. Hematogenous seeding usually occurs in the form of miliary tubercles; but sometimes larger foci do develop, and these are generally caseous. These large caseous foci have been demonstrated in the liver, spleen and brain, and in most instances they undergo anatomic healing by encapsulation and deposition of calcium. When skeletal tuberculosis develops, the caseous focus enlarges and undergoes liquefaction. In those cases in which spinal tuberculosis develops, the caseous focus in most instances lies near the intervertebral disk; it undergoes liquefaction and extends through the disk to involve the adjoining vertebrae.

The tuberculous process may develop in joints in two ways. It may occur through the rupture of an epiphysial tuberculous focus into the joint space. This process is designated as the osteal form, in contrast to the synovial form, in which the tuberculous process originates in the joint itself. There is no unanimity of opinion as to which mode of infection predominates. The tuberculous focus producing tuberculosis of the joint lies near the joint capsule or the cartilage and perforates into the joint space through either the cartilage or the synovial insertion.

Complications: Abscesses and Fistulas.—In all 13 cases of tuberculosis of the vertebral column there were accompanying abscesses in the region of the involved vertebrae. The extent of the paravertebral abscesses varied; in most instances it was limited to the vertebrae involved in the tuberculous process; this was true particularly when the tuberculous process was present in the dorsal region. In most instances the abscess was bilateral. Paravertebral abscesses in the lumbar portion of the spine, and sometimes those in the lower dorsal region, penetrated along the lateral side of the vertebral column and then continued along the sheath of the psoas muscle to form psoas abscesses. In a number of instances the abscess, following the course of blood vessels, perforated the skin in many areas to form fistulous tracts. In 1 case a paravertebral abscess lying lateral to a cervicodorsal area of tuberculosis ruptured into the upper lobe of the left lung. Three of the 13 patients with spinal tuberculosis had accompanying external pachymeningitis. In each of these cases there was a history of paraplegia during life.

In cases of tuberculosis of the joint liquefied material penetrates to the skin, perforating it in one or more areas to form fistulas. It may collect in the tissue spaces around the involved joint and extend for considerable distances along the fascial planes of the extremity before reaching and perforating the skin.

UROGENITAL TUBERCULOSIS

There were 10 children (11.1 per cent) with urogenital tuberculosis, 9 of whom were girls.

Renal Tuberculosis.—Three children (3.33 per cent) had renal tuberculosis; this is comparable to an incidence of 4.9 per cent in

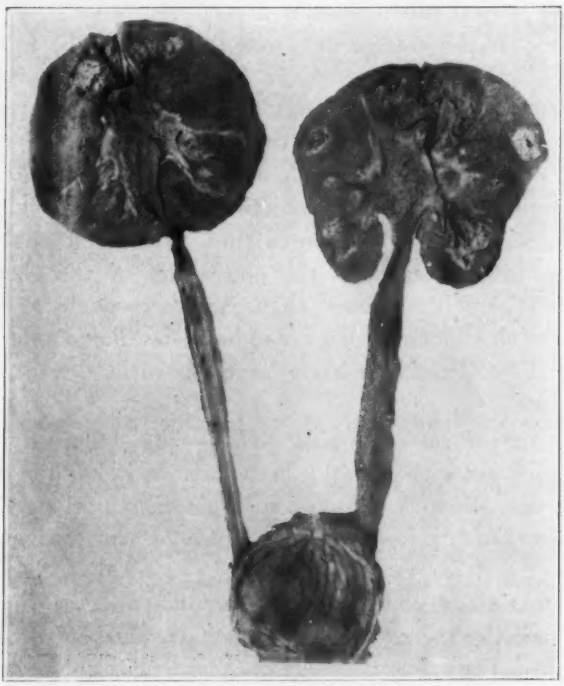

Fig. 3.—Bilateral renal tuberculosis in a white girl 18 months of age. The tuberculous cavities are more numerous on the left side. The left renal pelvis and the left ureter are dilated and contain tuberculous ulcers. The urinary bladder also contains ulcers.

patients of all age groups. One was an 11 year old boy who also had an extensive tuberculous involvement of the genital system. The 2 girls with renal tuberculosis showed no pathologic changes in the genital organs. In adults urogenital tuberculosis occurs much more frequently in men.

In 2 of the 3 children with renal tuberculosis the lesion was unilateral; in the other it was bilateral. In all 3 children there was an ulcerative process of the renal parenchyma similar to that seen in

tuberculosis of an isolated organ in adults. Each of the children had ulcers in the renal pelvis and the ureter of the affected side and tuberculous ulcers in the urinary bladder.

Genital Tuberculosis.—There were 8 children with genital tuberculosis in this series. Examination of 7 (14.9 per cent) of the 47 girls revealed tuberculosis of the fallopian tubes. This incidence is comparable to 9.1 per cent for tuberculosis in patients of all ages. One boy (2.3 per cent) had genital tuberculosis. This incidence (2.3 per cent) is in contrast to that (14.4 per cent) for tuberculous patients of all ages. Although this series is small, I feel justified in concluding that genital tuberculosis occurs with greater frequency in girls than in adults, while in boys genital tuberculosis is a rare occurrence.

I believe that the greater incidence in girls may be accounted for on the basis of anatomic differences in the male and female reproductive systems. I found that genital tuberculosis occurs with greatest frequency in the prostate in men and in the fallopian tubes in women. The tuberculous process in both organs develops by means of a hematogenous dissemination to the stromal tissue. The larger foci may have a caseous center. If these foci extend through the epithelial surface of the fallopian tube or through the epithelium of the glands of the prostate, the tuberculous process than extends through the organ. The prostate in the child does not appear to be as developed anatomically as the fallopian tube. The latter has a large free surface, while the former has small glands.

Tuberculosis of the Fallopian Tubes.—The fallopian tubes were involved in each girl with genital tuberculosis. In 1 child the tuberculous process was first discovered on microscopic examination. The wall of the tubes contained a few tubercles, some of which showed central caseation.

In the remaining 6 children, the tuberculous process was advanced, and the fallopian tubes. which were irregularly thickened, had a tortuous appearance. The tubes were soft in consistency, and on cross section the lumen was obliterated. The caseous process involved all layers of the walls. The serosal surface was studded with large and small caseous foci, and among them were patches of fibrin. The resultant peritonitis varied from one child to another. In several it was limited to the fallopian tubes, while in others it extended along the serous surfaces for variable distances.

A descending infection from the fallopian tubes to the uterus occurred in 3 children. The process was limited to the fundus and presented itself as an ulcer of the endometrium. In 2 patients the caseous salpingitis extended to the ovary, resulting in a tubo-ovarian mass, within which remnants of the tube and ovary were discernible on microscopic examination.

TUBERCULOUS MENINGITIS

Thirty-seven (41.1 per cent) of the children in this series died with tuberculous meningitis. This incidence is far greater than that in the older age groups. My observations substantiate the statement that tuberculous meningitis occurs frequently in children.

Age Distribution.—The youngest child in this group was 8 months of age. Siegel,[8] from his own studies and a review of the literature, reported a few cases of tuberculous meningitis in infants in the third month of life. One or more children with tuberculous meningitis were encountered in each year of life in this series. The greatest number (10) were in the second year of life.

Associated Pathologic Changes.—Tuberculous meningitis occurred in 5 children who had a fresh primary complex and acute generalized miliary tuberculosis secondary to it. In 3 of these children a tuberculoma had ruptured into the meninges.

Twelve of 35 children had a progressive primary complex. It is interesting to note that in a previous series of such children the incidence of tuberculous meningitis was almost the same (9 of 17 cases).

The greatest number of children (17) had a healing or a healed primary complex. In all but 3 children there was no other possible source for the development of meningitis. In addition to the primary complex, these 3 children had active tuberculosis of the skeletal system. The fact that neither generalized miliary tuberculosis nor any evidence of it was present at the time of the autopsy ruled out skeletal tuberculosis as a source of meningitis.

In only 3 children was tuberculous meningitis definitely associated with an active extrapulmonary tuberculous process. These children had acute generalized miliary tuberculosis. In 2 of them tuberculomas were observed in the brain, which were of the same anatomic age as the hematogenous foci in the apical portion of the lungs.

Pathogenesis.—Unfortunately, all the brains in this series were not studied to determine the mode of occurrence. This procedure would have entailed thin slicing of the brain after fixation and the study of all definite and suspicious foci. Since this investigation was not made in all cases an accurate evaluation is not possible.

Tuberculomas were seen in 27 of the brains examined. In 15 of these specimens an extension of the tuberculous focus to the overlying meninges was evident. In a few instances multiple foci extended to the overlying pia, though in most specimens there was extension of only one focus.

Tuberculomas were observed in 10 of the 15 brains of children with progressive primary complex. The foci which were the result of a

8. Siegel, M.: The Age Distribution and Pathogenesis of Tuberculous Meningitis in Children, Am. Rev. Tuberc. **32**:196-207 (Aug.) 1935.

hematogenous dissemination from the primary complex were more numerous than those resulting from an early abortive generalization or from a late generalization. In some instances the tuberculomas were so numerous that caseous foci studded all lobes of the parenchyma of the brain.

Tuberculous meningitis in 1 child resulted from the rupture of a liquefied tuberculous focus in the skull.

ISOLATED TUBERCULOSIS OF THE INTESTINE

Isolated tuberculosis of the intestine is characterized by the presence of extensive intestinal ulceration in the absence of pulmonary cavitation. Two cases were in this category. In 1 case, that of a 7 year old Negro girl, death followed an attempted removal of the cecum. There had been loss in weight for four months, accompanied with vomiting and abdominal pain. Roentgenographic studies had showed irregular filling defects in the ileocecal region. Autopsy revealed deep-seated ulcers in the ileum, cecum and ascending colon. Microscopic examination of these lesions showed typical tuberculous changes. The only other tuberculous sign was a healed primary complex in the lungs.

The other case was that of a white girl 22 months of age, whose mother had chronic pulmonary tuberculosis. The feces yielded tubercle bacilli on one examination. The child died of tuberculous meningitis. Autopsy revealed deep-seated ulcers in the jejunum, ileum, cecum and ascending, transverse and descending portions of the colon. The mesenteric lymph nodes were enlarged and contained caseous calcified areas. The only pulmonary lesions were a few miliary and acinous foci in the upper lobes. There was no evidence of a primary complex in the lungs.

The pathogenesis in these cases is of great interest. In the first case a new infection of the intestinal tract with bovine tubercle bacilli may have occurred. In the second case, the absence of a primary complex in the lungs and the presence of calcified foci in the mesenteric lymph nodes bring to mind the possibility of primary intestinal tuberculosis. In this instance the lymph node component healed while the intestinal lesion progressed.

TUBERCULOSIS ENDOCARDITIS

Davie,[9] Baker[10] and Mark[11] pointed out that tuberculosis of the endocardium, and especially of the valves, occurs infrequently. In 1938 Mark reported what is apparently the seventh proved case of isolated

9. Davie, T. B.: Tuberculous Verrucose Endocarditis, J. Path. & Bact. **43**:313-320 (Sept.) 1936.

10. Baker, R. D.: Endocardial Tuberculosis, Arch. Path. **19**:611-635 (May) 1935.

11. Mark, J.: Tuberculous Endocarditis of the Pulmonary Valve, Bull. Johns Hopkins Hosp. **63**:415-419 (Dec.) 1938.

valvular vegetations of definite tuberculous nature. Unquestionably my case meets all the criteria of tuberculous valvular endocarditis. The case was that of an 11 year old Negro girl who for nineteen months before death had complained of cough and weakness. There were caseous tuberculosis of the anterior leaflet of the mitral valve and of the leaflets of the aortic valve and tuberculous ulceration of the endocardium of the left ventricle. The involved portions yielded tubercle bacilli. The only other tuberculous lesions were fresh caseous foci in the liver and spleen and a healed primary complex.

One may speculate that at the time of the primary complex a hematogenous seeding resulted in subendocardial foci which progressed, while the primary complex underwent healing changes. The caseous foci in the liver and spleen were the result of a hematogenous seeding from the tuberculous endocarditis.

SUMMARY AND CONCLUSIONS

In a study based on a series of 90 fatal cases, the various anatomic changes deriving from tuberculosis are described as they are likely to be seen in children. The disease was present in its diverse forms: (1) the primary complex, (2) hematogenous tuberculosis and (3) chronic pulmonary tuberculosis. The relative frequency (22 per cent of all cases) of the last-named form of the disease is worthy of special notice, since it has not been sufficiently stressed that children are common victims of this allegedly adult form. Short discussions of the pathogenesis of each lesion are included, as well as relative incidences according to sex and race.

In this series, 67.8 per cent of the children were Negro, and the study showed that in persons of this race the progressive form of the primary complex is most likely to occur. For this reason, hematogenous forms of tuberculosis are most frequently encountered in Negroes.

In 41 per cent of the cases in this series the cause of death was tuberculous meningitis, and in 78 per cent of this number tuberculomas were present within the brain.

Case Reports

COMPRESSION OF THE TRACHEA BY AN ANOMALOUS INNOMINATE ARTERY

An Operation for Its Relief

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AND

EDWARD B. D. NEUHAUSER, M.D.

BOSTON

IN PREVIOUS communications[1] we described surgical technics for the alleviation of esophageal or tracheal obstructions which were caused by extrinsic pressure from a double aortic arch or from an anomalous right subclavian artery. In a brief way, we should like to summarize our experience with the successful surgical treatment of a similar condition in which the trachea was compressed by an innominate artery which lay in an unusual position.

For many decades anatomists and pathologists have been recording abnormalities of the aortic arch and the great vessels which arise from it. On several occasions clinicians[2] described the symptoms which can arise from such vascular malformations, making particular reference to the evidence of esophageal or tracheal obstruction. More recently the roentgenologist[3] has pointed the way for a rapid and rather accurate recognition of these abnormalities by roentgenographic visualization of the esophagus and trachea with contrast mediums. Now it would appear to be the responsibility of the surgeon to provide measures which will bring relief to some of these patients. While it is at once

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From the Surgical and Roentgenologic Services of the Children's Hospital, and the Departments of Surgery and Radiology of the Harvard Medical School.

1. *(a)* Gross, R. E.: Surgical Relief for Tracheal Obstruction from a Vascular Ring, New England J. Med. **223**:586 (Nov. 15) 1945; *(b)* Surgical Treatment for Dysphagia Lusoria, Ann. Surg. **124**:532 (Sept.) 1946. *(c)* Gross, R. E., and Ware, P. F.: The Surgical Significance of Aortic Arch Anomalies, Surg., Gynec. & Obst. **83**:435 (Oct.) 1946.

2. Bayford, D.: An Account of a Singular Case of Deglutition, Mem. M. Soc. London **2**:271, 1794. Sprague, H. B.; Ernlund, C. H., and Albright, F.: Clinical Aspects of Persistent Right Aortic Root, New England J. Med. **209**:679 (Oct. 5) 1933. Wolman, I. J.: Syndrome of Constricting Double Aortic Arch in Infancy: Report of Case, J. Pediat. **14**:527 (April) 1939. Gross and Ware.[1c]

3. Neuhauser, E. B. D.: The Roentgen Diagnosis of Double Aortic Arch and Other Anomalies of the Great Vessels, Am. J. Roentgenol. **51**:1 (July) 1946.

apparent that many of these intrathoracic vascular malformations are beyond the reach of surgical treatment because of insurmountable technical difficulties, nevertheless, it has become clear that a few of the arterial derangements can be changed by operative intervention and that pressure can be taken from the esophagus or trachea. Into the latter category of cases favorable for surgical treatment we should like to place the condition which is described in the following report.

REPORT OF A CASE

M. D. was born June 2, 1946 by a forceps delivery. Weight at birth was 8 pounds 2 ounces (3,685 Gm.). No abnormalities were noticed at the time, but during the following day the baby regurgitated all feedings. On the third day the child had a slight cough, a grunting and wheezing type of breathing and a mild degree of cyanosis. Because of these symptoms she was transferred to the Boston Floating Hospital, where she remained for more than four months. During this long period of observation there were occasional bouts of regurgitation or vomiting, but these gradually disappeared and seemed to be of no importance. During that stay in the hospital great anxiety was

Fig. 1.—Preoperative photograph of patient showing the opisthotonos and the hyperextension of the head. This position was spontaneously assumed by the baby; it appeared to minimize the respiratory distress.

caused by respiratory distress, which persisted but which varied in intensity from time to time. The breathing was always noisy and wheezing in character. It was discovered that the wheezing was much diminished when the child was placed in a position with the head in extreme hyperextension. Indeed, if left alone, the baby would struggle over onto her side so that the head could be brought spontaneously into hyperextension. There were frequent bouts of fever, the temperature rising to as much as 102 F. For the first month and a half there was usually a leukocytosis, the count ranging from 13,600 to 18,000. This evidence of infection was believed to come from a superimposed tracheitis and pneumonitis. On several occasions the child was ill enough to be placed in an oxygen tent—for as long as two weeks at a time. During one such episode her condition was so serious that her name was placed on the danger list. Roentgenographic examination with iodized oil U.S.P. showed a definite abnormality of the trachea. The child was transferred to the Children's Hospital for further study on October 14.

At the time of the transference to our care the baby weighed 10 pounds 3 ounces (4,621 Gm.) and appeared to be somewhat underdeveloped for her chronologic age. There was no cyanosis. The breathing was noisy, particularly during inspiration and

could be heard when the observer was 7 or 8 feet (213 to 244 cm.) away from the baby. Auscultation revealed loud wheezing and rasping sounds over the entire chest. The respiratory rate was elevated to 44 a minute. There was moderate suprasternal retraction during inspiration. The accessory muscles of respiration were being used vigorously. The child constantly lay on one side with the head in extreme hyperextension (fig. 1). When we attempted to place the baby on her back, she would become uncomfortable; respiratory distress would increase and she would wiggle until she could get over onto one side and hyperextend the head—a position which obviously produced maximum comfort. Any forcible attempt to move the baby's head into a flexed position seriously augmented the respiratory distress, whereas the resumption of the hyperextended state greatly eased the baby's symptoms.

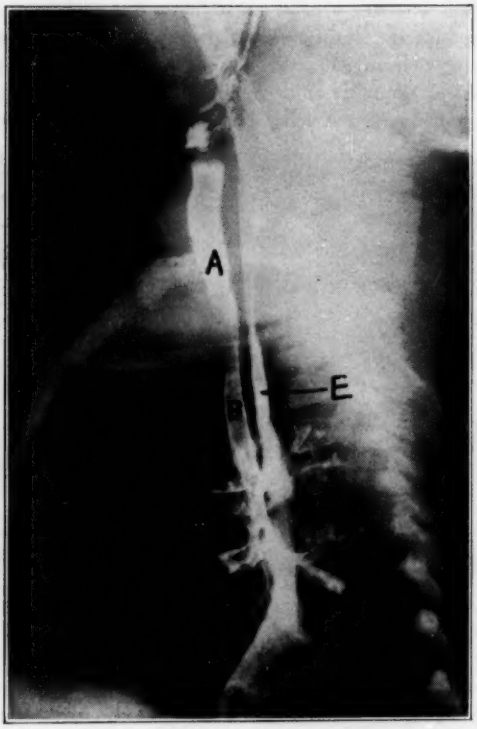

Fig. 2.—Lateral roentgenogram, with visualization of the trachea by means of iodized oil U.S.P. The trachea is decidedly narrowed between the points *A* and *B*, where there is an indentation on its anterior surface. (Some iodized oil has spilled over into the esophagus, *E*.).

Fluoroscopic examination of the chest showed no abnormality of the heart or lungs. The swallowing function appeared normal, and no extrensic pressure defect was evident in the esophagus filled with barium sulfate. Roentgenograms of the chest showed no abnormality in the anteroposterior projection, but in the lateral projection definite narrowing of the trachea could be seen. Iodized oil was instilled into the trachea for better visualization. In the anteroposterior view slight broadening of the trachea just below the thoracic inlet could be seen. In the lateral view an extrinsic pressure defect was present on the anterior aspect of the trachea (fig. 2). This defect was just above the level of the aortic arch and coursed obliquely upward from left to right. It was thought that this defect was produced by an aberrant artery arising on the left side of the aortic arch and passing obliquely in front of the trachea to its distribution on the right side.

Operation was undertaken October 17, with the infant under anesthesia induced by cyclopropane, using positive pressure through a tightly fitting face mask. The breathing could be made fairly satisfactory by placing a large sandbag under the chest and shoulders so that the head could drop back into pronounced extension. The thorax was opened through a left anterolateral incision, running below the breast and entering the chest in the interspace. To gain access to the trachea and the great vessels, the thymus gland was mobilized and about seven eighths of it was cut away and discarded. An excellent view was now obtained of the trachea and of the great vessels arising from the aortic arch (fig. 3*A*). The innominate artery arose from the aortic arch somewhat to the left of its normally expected position, and, indeed, this vessel had a common origin with the left common carotid artery. As the innominate artery coursed to the right, upward and backward, to reach the thoracic outlet, it forcibly pressed on the anterior and right anterolateral surfaces of the trachea in such a way as to deform this structure and reduce the size of its lumen. The innominate artery was momentarily pulled forward, which relieved the noisy respiration. (The tracheal pressure could have been com-

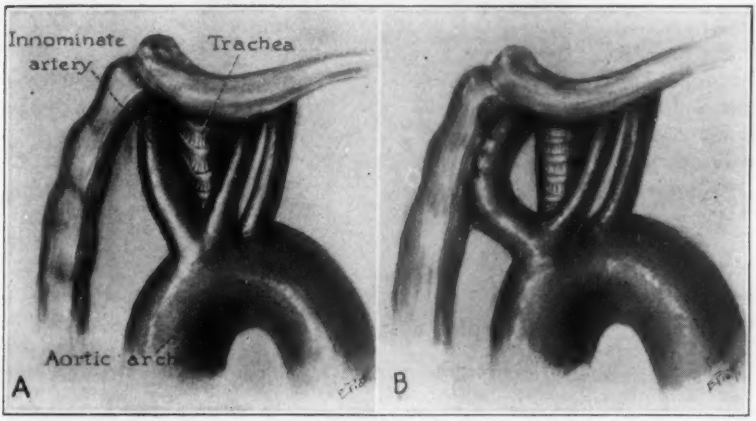

Fig. 3.—*A*, observation at operation through a left anterolateral approach. The thymus gland has been removed to expose the great vessels and trachea. The innominate artery arises from the aorta farther to the patient's left than is normal. This artery compresses and indents the anterior portion of the trachea. *B*, surgical procedure for relief of tracheal compression. The innominate artery is held forward by tacking its adventitia to the sternum with silk sutures.

pletely relieved by a division of the innominate artery, but we decided against this procedure because of the risk of producing cerebral ischemia.) It was decided to tack the innominate artery into a forward position by anchoring it to the back of the sternum. This step was accomplished by using fine silk sutures to grasp the adventitia of the vessel, as well as the periosteum of the posterior surface of the manubrium sterni. When these silk sutures were drawn taut, the artery was pulled forward, and there was no further contact between it and the trachea (fig. 3*B*). The chest was carefully closed, and the lung was reexpanded fully. At the end of the procedure the quality of the baby's respirations was definitely improved.

After the operation, the baby had an extremely satisfactory convalescence. The wound healed per primam. The respirations became normal in character and completely lost all the wheezing, rasping quality which they had before operation. The child no longer attempted to hold her head in hyperextension. On the sixth postoperative day bronchograms were made with iodized oil, and these showed great improvement in the appearance of the trachea. There was still a slight defect in the anterior wall of the

trachea. This defect did not have the appearance of indentation due to external compression; it was interpreted as representing a mild structural deformity of the trachea which had developed as a result of the external compression which had existed throughout the life of the baby prior to operation. The child was discharged from the hospital on the eighth postoperative day, and there have been no complaints referable to the respiratory tract since that time. She was last seen on Jan. 20, 1947 and was entirely asymptomatic.

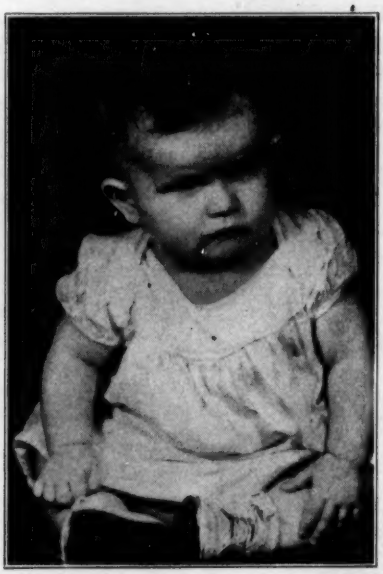

Fig. 4.—Photograph three months after operation. The child can breathe normally.

COMMENT

It is conceivable that the abnormality in the previously described case could have been tolerated without any surgical intervention, particularly if the baby could have been kept free of superimposed infections of the respiratory tract. It is possible that had the child not been operated on her growth and the shifting of organs within the chest might have allowed a readjustment to take place which would have minimized the tracheal compression. However, it is well to point out that in this baby, as in most infants with obstruction of the respiratory tract, recurring infection of the lower respiratory system developed, and experience has shown that such a series of events frequently has a fatal termination. Hence, we cannot escape the conclusion that tracheal obstruction should be alleviated whenever it is feasible to do so.

The relief of respiratory distress in our patient was most gratifying. It was accomplished by a procedure which was not particularly difficult to perform. This report is made in order to emphasize the fact that certain tracheal obstructions can be recognized by proper roentgenologic study and can be relieved by surgical attack on the underlying malformation. It is hardly necessary to add that the performance of such a task requires adequate facilities for undertaking explorations of the chest in small subjects.

300 Longwood Avenue.

ATRESIA OF THE TRICUSPID VALVE WITH TRANSPOSITION OF THE GREAT VESSELS

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AND

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IN VIEW OF the more hopeful approach to the problem of therapy of congenital heart disease resulting particularly from the recent development of newer surgical technics, the differential diagnosis of cardiac anomalies has become of more than academic importance. We feel, therefore, that it is pertinent to report on one of the more unusual congenital abnormalities of the heart, especially since it is an anomaly for which clinical diagnosis is possible. For this reason we report a case of atresia of the tricuspid valve with transposition of the great vessels in an infant 6 months of age.

REPORT OF A CASE

C. C., a white boy, was admitted to the pediatric service of the Mount Sinai Hospital on March 12, 1946, at the age of 6½ months. He was born after a normal pregnancy and delivery, weighing 3,180 Gm. He was breast fed for two weeks and was then started on an evaporated milk formula. His past history was noncontributory except that, according to his parents, he would "occasionally breathe heavily."

The day before admission to the hospital he refused or regurgitated most of his feedings, had five loose bowel movements, was irritable and felt warm to the touch. The following morning he was brought to the hospital. On physical examination, he appeared to be poorly developed, undernourished and acutely, but not severely, ill. He was somewhat dyspneic and pale and had cyanosis of the mucous membranes and nail beds. Hydration was good. The temperature was 103 F., the pulse rate was 160 and the respiratory rate 70. The left tympanic membrane was red and full in the region of Shrapnell's membrane. The right tympanic membrane was reddened but not full. There were diminished resonance and high-pitched breath sounds over the midportion of the right lung posteriorly. No rales were audible. The heart was somewhat enlarged, and a low-pitched, blowing systolic murmur was heard along the left sternal border. The abdomen was not distended. The liver and spleen were within normal limits. The remainder of the physical examination showed nothing abnormal.

Laboratory studies made on his admission to the hospital showed leukocytosis, with a count of 21,000 cells, 60 per cent of which were polymorphonuclear neutrophils. The hemoglobin concentration was 14 Gm. per hundred cubic centimeters, and the hematocrit reading was 36. The carbon dioxide-combining power was 42 volumes per

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From the Pediatric Service of Dr. Murray H. Bass, the Mount Sinai Hospital, New York.

cent. Total protein measured 3.7 mg. per hundred cubic centimeters. Urinalysis showed nothing remarkable. Roentgenographic studies revealed enlargement of the heart, especially to the right. The markings of the lungs were prominent, especially on the right side, and an infiltration of the mesial aspect of the upper lobe of the right lung was visible.

A diagnosis was made of pneumonia of the upper lobe of the right lung in an infant with congenital malformation of the heart. He received 0.2 Gm. of sulfadiazine per kilogram of body weight and twice that amount of sodium bicarbonate. Twenty-four hours after admission the child appeared toxic. His temperature had risen to 105 F. Because the dyspnea was more pronounced, he was placed in an oxygen tent. Culture of blood taken at that time was later reported as yielding no organisms. In addition to the sulfadiazine, 10,000 units of penicillin was given intramuscularly every three hours.

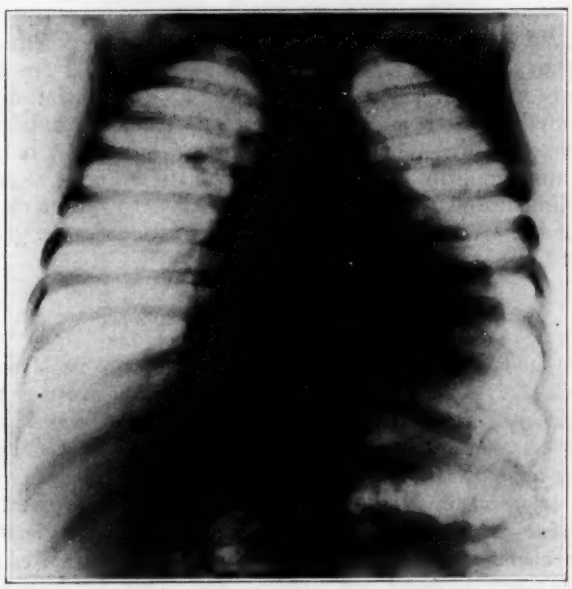

Fig. 1.—Roentgenogram of the chest, posteroanterior view. Enlargement of the heart, especially to the right; prominence of markings of the lungs, especially on the right side, and infiltration of the mesial aspect of the upper lobe of the right lung are shown.

On the third day the infant's condition appeared improved. The temperature was down to 103 F., and he began taking his feedings well. The culture of material from the nose and throat taken on admission revealed Staphylococcus albus B and Staphylococcus aureus A. Since the infant had hypoproteinemia, a plasma transfusion was given, but the procedure was interrupted after 60 cc. had been administered, because of evidence of heart failure. He became extremely dyspneic, pale and slightly cyanotic. The liver could be felt at the level of the umbilicus. He was kept in the oxygen tent and was watched carefully for further evidence of cardiac failure. By the fifth day in the hospital the infant appeared much better, and his temperature was normal. Dyspnea was slight, and he took his feedings well. The lungs were almost clear, and the liver had receded to about 2 cm. below the costal margin. The white blood cell count had dropped

to 12,000 per cubic millimeter. As the improvement persisted, sulfadiazine was discontinued after the sixth day and penicillin after the eighth day. On the tenth day in the hospital evidence of heart failure recurred, the liver again being felt at the level of the umbilicus. A roentgenogram of the chest at this time revealed no change in the heart and vascular markings, but showed resolution of the pulmonary consolidation. The electrocardiogram demonstrated left axis deviation; the P waves of leads II and III

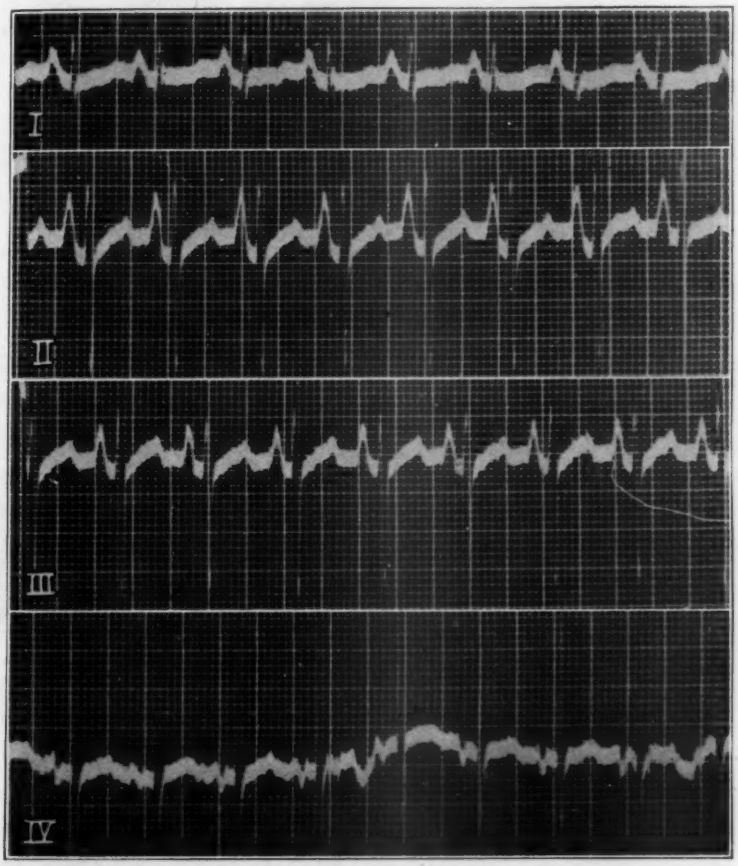

Fig. 2.—Electrocardiogram showing left axis deviation. The leads I through IV are in order, from the top downward. The P waves of leads II and III are peaked and tall; the QRS complex in lead I is notched, and the RS-T segments of leads II and III are slightly depressed.

were peaked and tall; the QRS interval in lead I was notched, and the RS-T segments of leads II and III were slightly depressed. The interpretation stated: "The left axis deviation is unusual in children of this age group. The peaked P waves are often observed with enlargement of the auricles."

The patient was digitalized with "digifolin," a dose equivalent to 0.15 Gm. of digitalis U.S.P. per 5 Kg. of body weight being given intramuscularly. After digitaliza-

tion he was kept on a daily maintenance dose of 0.25 cc. of "digifolin," i. e., 0.0125 Gm. of digitalis, given intramuscularly. Two oral dextrose tolerance tests, using 3 Gm. of dextrose per kilogram of body weight, gave normal curves. Acetone was not present in the urine on repeated examination. Fluoroscopic studies showed no evidence of displacement of the esophagus. A second electrocardiogram, taken on the seventeenth day in

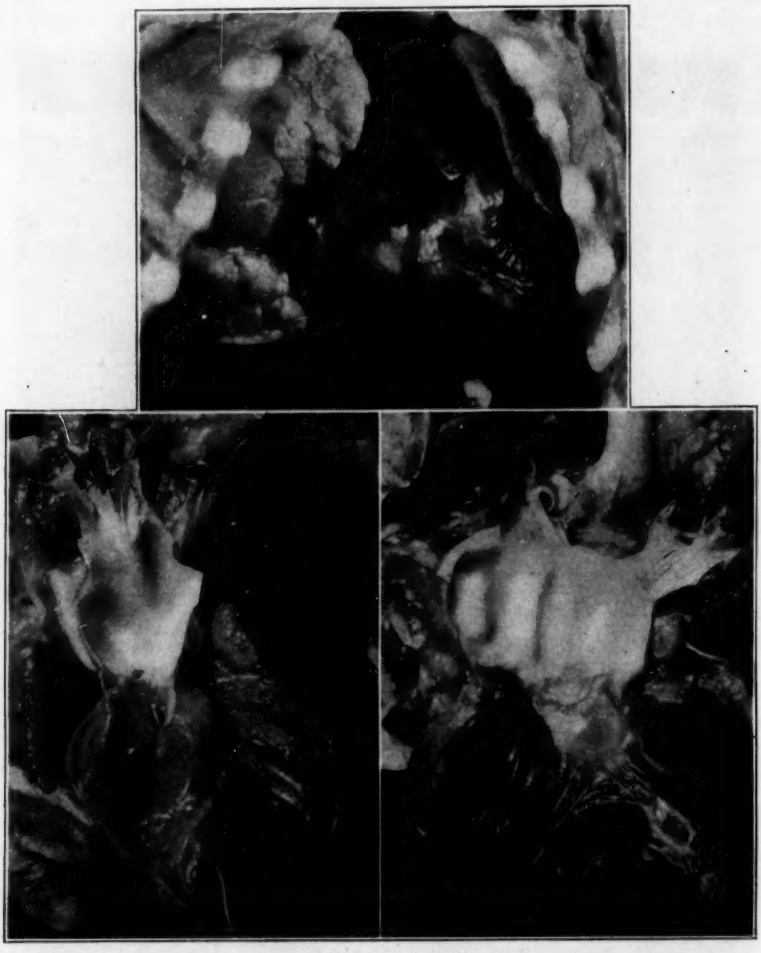

Fig. 3.—In *A*, the heart of the infant with the elongated transverse diameter and the large right atrium is shown in situ. In *B*, a probe has been placed in the defect in the interventricular septum. The aorta is seen arising from a hypoplastic right ventricle. In *C* is shown the greatly hypertrophied left ventricle, from which a dilated pulmonary artery arises.

the hospital, showed an inverted T wave of lowered voltage in leads I, II, III and IV and a depressed RS-T segment. These changes were interpreted as due to digitalization.

On the twenty-eighth day in the hospital the infant had an episode of diarrhea. He was starved for twenty-four hours, and clyses were given. Although a transfusion

of 60 cc. of blood was given slowly, he again, twelve hours later, had severe heart failure. He recovered somewhat from this acute episode but remained in a state of moderate heart failure, which gradually became worse, until he died on the forty-fourth day in the hospital.

Autopsy (Dr. L. Strauss).—The heart was described as follows: "The heart is considerably enlarged, and its shape is altered owing to elongation of its transverse diameter. Its right border and part of the base are formed by the disproportionately large right atrium, which also makes up about one-half the anterior surface of the heart. The apex and the left border are formed by the left ventricle. The demarcation between the right atrium and the ventricular portion of the heart is vertical in situ. The posterior portion of the heart is formed by the left atrium, as well as the left ventricle. On the anterior surface the usual demarcation of the septum dividing the right from the left side of the heart is missing. Instead, there is a shallow groove in the upper part of the anterior wall which is directed obliquely to the right and away from the course of the descending anterior branch of the left coronary artery. Above this groove there is a slight bulge in the ventricular wall, demarcating a small triangular segment. The surface of the heart is free of fat tissue and shows prominent, engorged veins. Its consistency is firm. Anteriorly, from the base of the heart, rises the aorta, the trunk of which measures 1 cm. in diameter. It gives off its main branches in the usual order. The main trunk of the pulmonary artery lies behind the aorta. Its diameter is at is at least twice that of the aorta. The ductus arteriosus is visible as a short cord, measuring 3 mm. in width externally. The superior and inferior venae cavae enter the right atrium in the usual way. The inferior vena cava is dilated and its wall thickened. The right atrium is a large chamber with uniformly thickened walls measuring 2.5 mm. and showing prominent trabeculae carneae and a thickened, smooth, gray endocardium. The auricular appendage is also greatly dilated. There is a patent ostium secundum, which measures 1 cm. in its largest diameter. The coronary sinus is normally located. The right atrioventricular ostium is absent and, as a result, there is complete atresia of the tricuspid valve. The left atrium is slightly dilated. Its wall is not thickened. The pulmonary veins enter the left atrium in the usual fashion. The mitral valve is normally formed and consists of thin, transparent leaflets. The chordae tendineae insert normally. The papillary muscles are bulky. The mitral ring measures 5.2 cm. in circumference. There is conspicuous hypertrophy of the left ventricle, the wall of which measures up to 12 mm. in thickness. Its longitudinal diameter is 3.8 cm. The myocardium is firm and red. The mural endocardium is thin and delicate. There is moderate dilatation of the left ventricle. The interventricular septum shows in its anterior muscular portion a defect, which measures 5 mm. in diameter. The pulmonary artery arises from the left ventricle. The pulmonary valve is normally formed. The pulmonic ring is 3.2 cm. in circumference. The main trunk and the branches of the pulmonary artery are strikingly dilated. The right ventricle consists of a small chamber located in the upper anterior portion of the heart. It communicates with the remainder of the heart through the defect in the interventricular septum. Its wall is comparatively thick and fleshy, measuring 9 mm. Its endocardium is somewhat thickened over the area lying opposite the defect in the interventricular septum. Its largest diameter measures 1.8 cm. From this tiny chamber rises the aorta, which measures 2.7 cm. in circumference at its origin. The aortic valve is normally formed, and the coronary ostiums are located in their usual sites. The coronary arteries have a normal course and distribution. The ascending aorta is slightly dilated, while the descending aorta has a circumference of only 1.2 cm. The lumen of the ductus arteriosus is of pinpoint size."

The complete postmortem diagnosis was: complete transposition of the great vessels with defect in the interventricular septum; atresia of the tricuspid valve; dilatation and hypertrophy of the right atrium; persisten ostium secundum; hypoplasia of the right ventricle; dilatation of the pulmonary artery and its branches; hypertrophy of the left ventricle; confluent bronchopneumonia in the lower lobe of the left lung; pulmonary emphysema and focal atelectasis; congestion and fatty changes in the liver; dilatation and thickening of the inferior vena cava and of the hepatic veins; petechiae of the pleura and pericardium, and aberrant pancreatic tissue in the wall of the stomach.

COMMENT

A review of the literature revealed that 34 cases of atresia of the tricuspid valve had been reported up to 1946. Maude Abbott[1] found 25 cases of atresia of the tricuspid valve, which are included in her analysis of 1,000 cases of congenital heart disease. Since her publication, cases have been reported by Taussig[2] and Brown,[3] in 1936; Roberts,[4] in 1937; Sakaki,[5] in 1938; Harris and Farber[6] and Holder and Pick,[7] in 1939; Eisenberg and Gibson,[8] in 1941, and Manhoff and Howe,[9] in 1945.

These cases can be divided into two types: (1) those without transposition of the great vessels, in which cyanosis is usually severe and which belong in the class of extreme morbus caeruleus, and (2) those with transposition of the great vessels, in which the cyanosis is less severe.

The great majority of the cases in the literature belong to the first group. However, of the cases in the second group none was exactly similar to ours. In Manhoff and Howe's case[9] atresia of the pulmonary valve and patent ductus arteriosus were associated. In Hedinger's interesting case[10] the lesion was similar to that in our case except that

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2. Taussig, H.: The Chemical and Pathological Findings in Congenital Malformations of the Heart Due to Defective Development of the Right Ventricle Associated with Tricuspid Atresia or Hypoplasia, Bull. Johns Hopkins Hosp. **59**:435, 1936.

3. Brown, J. W.: Congenital Tricuspid Atresia, Arch. Dis. Childhood **11**:275, 1936.

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6. Harris, J. S., and Farber, S.: Transposition of the Great Cardiac Vessels, with Special Reference to the Phylogenetic Theory of Spitzer, Arch. Path. **28**:427 (Oct.) 1939.

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8. Eisenberg, G., and Gibson, S.: Congenital Heart Disease and the Electrocardiogram, J. Pediat. **19**:452, 1941

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both the great vessels arose from the left ventricle. Eisenberg and Gibson's case[8] was also similar to ours, except that the right ventricle was completely absent.

From a study of the present case and the others reported, it becomes apparent that this type of malformation can be recognized during life if its possibility is borne in mind. Of primary importance in establishing its diagnosis are the electrocardiogram and the roentgenogram. The former shows alterations in the P wave consisting of an increase in height and notching, which are evidence of enlargement of an auricle. In addition, there is left axis deviation. Atresia of the tricuspid valve is the only congenital malformation in cases of the cyanotic type which gives left axis deviation. The roentgenogram shows an enlargement of the cardiac shadow, usually with absence of the pulmonary conus in the anteroposterior view. In the left anterior oblique position the absence of the cardiac shadow anterior to the aorta confirms the presence of a hypoplastic right ventricle. The aforementioned diagnostic characteristics, namely, the electrocardiographic and roentgenographic findings, indicate only the presence of atresia of the tricuspid valve. However, the fact that these patients have only a mild degree of cyanosis, rather than a typical morbus caeruleus, leads one to suspect transposition of the great vessels as an associated lesion.

According to Abbott,[1] the presence of transposition of great vessels is a favorable factor in the prognosis of atresia of the tricuspid valve. Hedinger[10] reported the case of a woman who lived to the age of 56 without cardiac symptoms and in whom postmortem examination revealed an atresia of the tricuspid valve with incomplete transposition of the great vessels, the aorta and the pulmonary artery, arising from the left ventricle.

The early fatal outcome in our case may have been due, at least in part, to the presence of a dilated pulmonary artery and of a relatively hypoplastic aorta.

SUMMARY

A case of atresia of the tricuspid valve and transposition of the great vessels in an infant 6 months of age is reported.

The possibility of establishing a correct diagnosis clinically is discussed.

1 East One-Hundredth Street.

GRANULOCYTOPENIA AND DEATH FOLLOWING THE USE OF TRIMETHADIONE

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AND

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DES MOINES, IOWA

TRIMETHADIONE N.N.R. ("tridione") has been used in man as an anticonvulsant drug since 1945. It has been found of greatest value in treatment of petit mal and psychomotor seizures. Toxic symptoms were reported by Lennox,[1] DeJong,[2] Richards and Everett,[3] Perlstein and Andelman[4] and Greaves,[5] but only 2 deaths following its use have been reported to date. These 2 deaths and the case recorded by Greaves are the only reported instances showing a toxic effect on the blood. Greaves's patient was a woman who took trimethadione in addition to phenobarbital and bromides. The last two drugs she had taken for years without ill effect. After only three weeks of trimethadione, her white blood cell count was 900, with 52 neutrophils, 42 lymphocytes and 6 mononuclear forms. Eight days after use of trimethadione was stopped, her white cell count returned to 5,000, but when the drug was resumed her white cell count fell within eight days to 900, with 13 neutrophils, 80 lymphocytes, 6 mononuclear forms and 1 eosinophil. Fortunately, the count returned in nine days to 6,250, and one month later she had 68 neutrophils, 27 lymphocytes, 1 mononuclear form and 4 eosinophils.

Harrison and associates[6] reported a case of fatal aplastic anemia after the use of trimethadione and a hydantoin. Trimethadione had been used for seven and a half months and methylphenylethyl hydantoin for six months. Mackay and Gottstein[7] reported a death from

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From the Raymond Blank Memorial Hospital for Children.

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5. Greaves, R. J.: Sensitivity to Tridione, Correspondence, J.A.M.A. **132**:44 (Sept. 7) 1946.

6. Harrison, F. F.; Johnson, R. D., and Ayer, D.: Fatal Aplastic Anemia Following Use of Tridione and a Hydantoin, J.A.M.A. **132**:11 (Sept. 7) 1946.

7. Mackay, R. P., and Gottstein, W. K.: Aplastic Anemia and Agranulocytosis Following Tridione: A Fatal Case, J.A.M.A. **132**:13 (Sept. 7) 1946.

aplastic anemia and granulocytopenia following the administration of trimethadione. Their patient had taken phenobarbital for nineteen years without ill effect and trimethadione for ten months. The case to be reported is similar to that of Greaves in that evidences of toxicity to the blood appeared shortly (three weeks) after treatment with the drug was begun. However, death occurred in this case.

REPORT OF A CASE

History.—R. W., a boy 6½ years of age, was admitted to the hospital on April 27, 1946 and died May 16. His complaints were fever for two days, with a rise in temperature to 104.5 F., and vomiting for eight hours. He was seen at home the day of admission to the hospital, and the attending physician noted a red throat, for which he prescribed sulfadiazine, all of which the child vomited.

Birth was essentially normal. He had a normal delivery after a short labor, was born at full term and weighed 6 pounds 4 ounces (2,835 Gm.). The neonatal period was uneventful. From the first he presented a feeding problem, with frequent and intermittent vomiting. He was somewhat slow in development, sat alone at 11 months of age, walked with support at 17 months and walked alone at 22 months. After the onset of his convulsions, his intelligence level deteriorated, so that at the time of his last illness he showed a low grade mental deficiency.

At the age of 4 years he had his first convulsion without fever. This attack was followed shortly by many others, at first of the grand mal type only and then, after attempted regulation with diphenylhydantoin sodium U.S.P. ("dilantin"), of the petit mal type also. The diagnosis of epilepsy was made, possibly on the basis of cerebral palsy or some cerebral anomaly. When he was 4 years of age, treatment was started with phenobarbital and was changed to diphenylhydantoin sodium and a ketogenic diet two months later. From that time on he had, alone or in combination, phenobarbital, diphenylhydantoin sodium or tablets of three bromides N. F. Although he was given a ketogenic diet when he was regulated in the hospital, his cooperation was poor in this respect at home. Three weeks before his last admission to the hospital administration of trimethadione was begun. It is a question how much of this drug he actually ingested, because he refused some of it and vomited two or three doses. This type of behavior had been characteristic from infancy. The day of admission to the hospital, he vomited everything he took by mouth. Trimethadione was added because the diphenylhydatoin sodium, phenobarbital and ketogenic diet did not control the petit mal attacks.

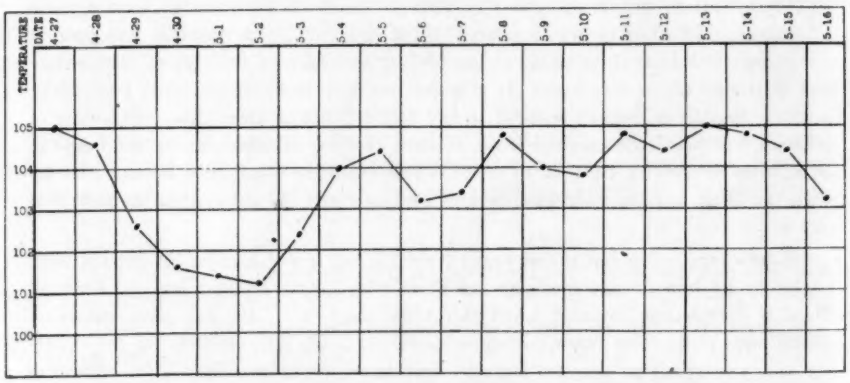
Final Illness.—His last illness began April 25, but it was because his parents were unable to get him to take medicine and fluids that he was brought into the hospital. Physical examination revealed a red throat and high fever. He was given penicillin, 30,000 units every three hours, intramuscularly and fluids intravenously for the vomiting and accompanying dehydration. His first blood count two days after admission showed 2,700 white cells with 98 lymphocytes and 2 neutrophils, 2,790,000 red cells and 9.6 Gm. of hemoglobin per hundred cubic centimeters.

Treatment and Course.—His course in the hospital was characterized by fever every day with the temperature usually 103 F. or more but varying between 101 and 105 F., and an ever present red throat without ulceration. After two days in the hospital, the ear drums became reddened, and pneumonia involving the upper lobe of the right lung appeared during the last four days of life. His spleen was never palpable; his

liver was barely felt, but a few slightly enlarged lymph nodes were present. Patches of erythema developed with some hemorrhage into them on the areas of friction and in the spots where penicillin had been given in the buttocks. These patches practically disappeared at the time his white cell count increased to 2,000. He was given phenobarbital for the first four days and then tablets of three bromides were administered. Crude liver extract, vitamin B complex, thiamine hydrochloride, ascorbic acid and one blood transfusion had no beneficial effect on his white cell count. In the accompanying table the essential laboratory data are recorded.

Summary of Observations on Patient

Date	Red Blood Cells	Hemoglobin, Gm./100 Cc.	White Blood Cells	Polymorphonuclear Leukocytes, Per Cent	Lymphocytes, Per Cent	Platelet Count	Other Data
4/29	2,790,000	9.6	2,700	2	98		
4/30	2,800,000	7.5	2,700	4	96	Adequate (smear)	.....
5/4	2,690,000	9.3	1,500	1	99	.....	Blood transfusion, 250 cc.
5/5	.....	...	1,100	..	100	.....	.....
5/6	3,520,000	11.3	1,300	..	100	Adequate (smear)	.....
5/9	3,580,000	11.3	1,000	..	100	.....	Blood culture, negative for pathogens
5/10	.....	...	1,100	..	...	.....	.....
5/11	3,330,000	...	1,500	..	...	266,400	.....
5/12	.....	...	....	..	...	.....	Bone marrow puncture
5/13	.....	...	2,000	..	...	.....	.....
5/14	.....	...	750	..	...	.....	.....
5/15	3,000,000	8.0	500	..	...	.....	Smear of buffy coat of blood
5/16	Death	...	....	..	...	.....	.....



Graph showing clinical record of highest temperature for each of the days in the hospital in the case of a 6½ year old boy with granulocytopenia following the use of trimethadione N.N.R.

Blood smears taken April 30 and May 5 were examined by the pathologist, who reported a normochromic anemia, an adequate number of platelets, absence of immature leukocytes and pronounced granulocytopenia. On May 15 he examined a smear made from the buffy coat of blood and stated that nearly all the cells were large and small lymphocytes, but that some extensively vacuolated toxic neutrophils were also present,

with no stem cells. The sternal marrow obtained on May 12 was reported by a hematologist as showing a few stem cells, evidence of erythropoiesis, including mitosis of the red cell series, a few premyelocytes and an occasional myelocyte, numerous small lymphocytes and blood platelets. He stated that the bone marrow did not have the appearance characteristic of leukemia or aplastic anemia and that the reduction in the myeloid series suggested granulocytopenia.

Other studies were reported as follows: The Kahn and Kline reactions of the blood were negative. Two urinalyses on April 28 and May 6 showed a high specific gravity, a 4 plus reaction for acetone, few or rare pus cells and an occasional red cell. A roentgenogram of the chest on May 13 showed pneumonia of the upper lobe of the right lung. The graph presents the highest temperature readings for each of the days in the hospital.

Necropsy Report.—Permission was obtained for only a partial necropsy, limited to a small abdominal incision. The liver was large and pale, estimated to be one-third larger than normal, and the lymph nodes were slightly enlarged. The kidneys and the intestine appeared normal. A section of vertebra showed scanty and thin marrow, which microscopic examination revealed to be poor in cells, with evidence of moderate fibrosis and a relative increase in lymphocytes. Microscopic sections of a lymph node, the spleen and the liver showed nothing abnormal. In the pathologist's opinion aplastic anemia was the most likely diagnosis. He expressed the belief that had the child lived longer the other manifestations of aplasia of the bone marrow might have become more apparent.

COMMENT

Inasmuch as this child had had one, and usually two, of the anticonvulsant drugs phenobarbital, diphenylhydantoin sodium and tablets of three bromides for two and a half years and had taken trimethadione for only three weeks, we felt that the trimethadione was the most likely cause of his granulocytopenia. From experience with other drugs, it is known that a toxic effect on blood cells resulting in their reduction may be not so much a matter of massiveness of dose or of long-continued use as one of individual sensitivity, in which even relatively small amounts of a drug may bring about the undesirable results. The patient did not keep down any of the sulfadiazine given him at home the day of admission to the hospital. Penicillin has not been reported to be a cause of depression of the blood cells. His red throat was undoubtedly on the basis of granulocytopenia. His cutaneous lesions may possibly have been due to penicillin, since they occurred also at the sites of inoculation, or they may have been the result of the granulocytopenia. His pneumonia developed while penicillin was being given, and his failure to recover from it may have been because of too few granulocytes to combat the disease.

The outstanding change in the cells of the blood in this patient was in the white cells, both in their total number and in the almost complete disappearance of the granulocytes. The change in the red series was slight, and the response to the small blood transfusion was good and was sustained, even after seven days. The fall in the hemoglobin value at the end may be explainable on the basis of the pneumonia which occurred terminally. The platelet studies always showed normal values.

Clinically, therefore, the diagnosis of granulocytopenia seemed to coincide most closely with the available evidence.

Whether a clinical blood picture of aplastic anemia would have developed in this child had he lived longer, we do not know. Sections from one bone, a vertebra, taken post mortem showed changes suggestive of this condition, but bone marrow from the sternum only five days before death did not indicate it.

Mackay and Gottstein recommended that blood counts be made frequently, at least every month, and that patients be warned of possible toxic symptoms. We should like to suggest that early in the giving of the drug blood counts be made at least once a week.

Since trimethadione is a comparatively new drug, we feel it important that any unusual experiences following its use should be recorded in order that frequency and severity of any possible toxic effects may become known.

SUMMARY

In a child, aged 6½ years, who had taken phenobarbital, diphenylhydantoin sodium and/or bromides for two and a half years and trimethadione for only three weeks, granulocytopenia developed, and the child died twenty-two days after the first symptom of fever. Material obtained by bone marrow puncture and blood smears gave evidence supporting the diagnosis.

It is suggested that patients placed under treatment with trimethadione have blood counts made at weekly intervals, at least for a time.

704 Equitable Building (9).

Progress in Pediatrics

LARGE SOLITARY PANCREATIC CYST AND OTHER DEVELOPMENTAL ERRORS IN A PREMATURE INFANT

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Our case not only is of anatomicopathologic interest because of the rarity of the condition but also has a clinical aspect. For these reasons we have thought it worth recording.

REPORT OF A CASE

Vera K., born on Oct. 16, 1946, was the first child of healthy parents. She was six weeks premature, the weight at birth being 2,000 Gm. There was no asphyxia. The right foot had six toes; no other anomalies were seen. The mother's pregnancy had been undisturbed.

On the second day the child was admitted to St. John's Hospital because of her premature birth. It was noted that she had difficulty in nursing and vomited frequently. Meconium appeared in the napkins.

On examination, on October 19, the child was whining as though in pain. The facies forboded mental debility. Slight icterus was present. In addition to the polydactyly, there was dystopia ani anterior, the anus being situated quite near the vulva. The abdomen was distended, with slightly edematous skin. There was no peristalsis. Percussion revealed dulness except in the epigastric region. The liver and spleen were not palpable. The heart and lungs presented no anomalies. The fontanel was under normal tension. There was no coccygeal fovea. Lines in the palms were normal. The infant was afebrile. A catheter introduced into the mouth reached the stomach without difficulty.

On the evening of October 20, a roentgenogram of the abdomen was made after a barium sulfate meal. It showed that the stomach contained a small quantity of barium sulfate, otherwise, the entire abdominal region was represented by a large shadow, obliterating the normal picture of the intestine. A roentgenogram made on the next day revealed the presence of the barium in the intestine in the pelvis minor, and the following day the barium appeared in the napkin.

An examination of the blood made on October 21 showed a hemoglobin content of 140 per cent, a red cell count of 6,420,000 and a white cell count of 11,600. Differential formula was as follows: eosinophils, 4 per cent; band forms, 7 per cent; polymorpho-

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nuclear leukocytes, 36 per cent; lymphocytes, 49 per cent; monocytes, 3 per cent and myelocytes, 1 per cent. Thrombocytes were present in a normal quantity. There were no nucleated red blood cells. Many of the leukocytes were degenerated and presented toxic granules. Large forms of the lymphocytes were fairly numerous, and some of them resembled the lymphocytes in infectious mononucleosis (Pfeiffer's glandular fever). (We have made several control blood counts on newborn infants and have encountered the same forms in a greater or lesser number, so that this finding presented nothing abnormal.)

On October 23 the vomiting was still present. Feeding was difficult, and the child became cyanotic during and after the feeding. She died on October 24.

Autopsy Observations.—Autopsy, performed two and a half hours after death, revealed the following changes: The skin and the subcutaneous layer of fat were atrophic. When the peritoneal cavity was opened, a bluish gray tumor the size of a grapefruit was observed. On its surface were ectatic blood vessels, and it contained fluid. The liver and stomach covered the superior part of the cyst. The spleen was not visible; of the intestine only a portion of the duodenum was to be seen. It ran transversely over the tumor and downward to the right. The rest of the contracted intestine was displaced downward to the right.

At this stage of the examination the surgeon of the hospital, Dr. E. A. Immink, was asked for his opinion. He suggested the possibility of the tumor being a pancreatic cyst. A small incision was made in the cyst, and about 300 cc. of clear yellow fluid was evacuated and kept for further examination. After the cyst had collapsed, it was clear that it was embedded in the ligamentum gastrocolicum, and Dr. Immink's diagnosis was confirmed. The cyst was freed from the ligament. There was a fairly large quantity of flattened pancreatic tissue on the upper surface of the sac. The rest of the abdominal organs appeared normal on macroscopic examination. The bladder was observed in the pelvis minor and was in contraction. The uterus and ovaries did not present any anomalies.

Of the thoracic organs, the heart proved to be normal. The thymus was of ordinary size. The right lung had only two lobes. In the lower parts of the lungs there were portions of dark violet appearance. Moreover, in the upper lobes of each lung were scattered small white spots. The cerebral hemispheres exhibited normal convolutions, but when the brain was taken from the skull a gelatinous mass escaped from the region of the cerebellum. Further macroscopic examination of the cerebellum revealed a noteworthy enlargement of the cisterna magna, which on both sides indented the cerebellar hemispheres and flattened the vermis. As a result, the fourth ventricle and the aqueduct of Sylvius were widened. The arachnoid of the cisterna magna was somewhat opaque.

Microscopic examination revealed arachnoiditis with neoformation of blood vessels. The gelatinous mass mentioned previously had escaped from the large cisterna magna.

The fluid of the pancreatic cyst had a specific gravity of 1.008 and contained less than 0.025 Gm. per hundred cubic centimeters of albumin, according to the method of Esbach. Rivalta's test gave a negative reaction. Dr. R. R. Rochat, of the Hague, reported that lipase and trypsin were present in the contents of the pancreatic sac, whereas diastase was lacking.

Macroscopic examination of the cyst showed on the smooth inner surface the opening of the pancreatic duct, which proved to be patent, and several very small pores. The common bile duct had widened; the papilla of Vater was clearly seen. The part of the duodenum containing the papilla of Vater and both ducts was excised for serial sections.

From the cyst two sections were taken for microscopic examination, which showed that the wall of the cyst was formed of fibrous connective tissue. It was lined with cubical epithelium which for the most part had loosened. There was a difference in the

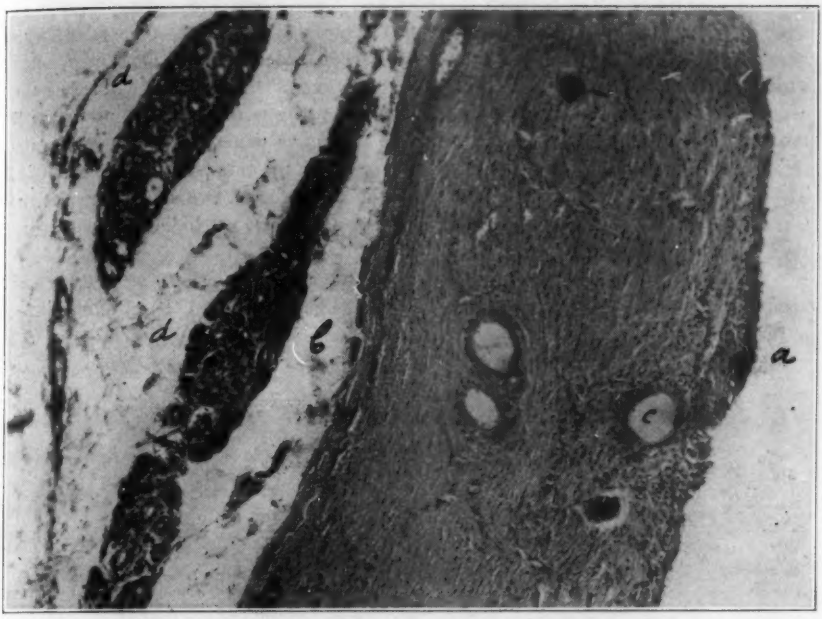

Fig. 1.—Photomicrograph of wall of cystic sac, showing *(a)* inner surface, *(b)* outer surface, *(c)* tubules and ductlike formations and *(d)* strands of pancreatic tissue.

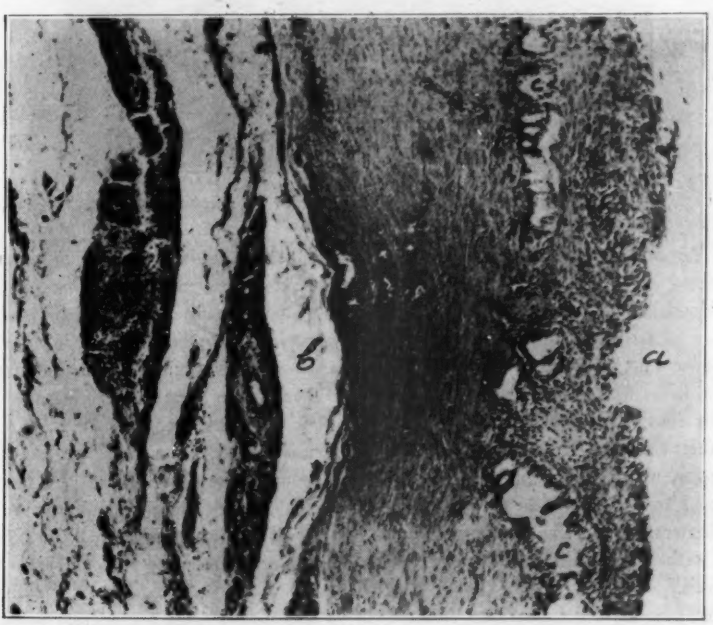

Fig. 2.—Photomicrograph of wall of sac, showing *(a)* inner surface, *(b)* outer surface with strands of pancreatic tissue and *(c)* widened, ductlike formations.

layer of connective tissue between its inner and outer parts. The outer part was of straight, closely packed fibers, while those of the inner part were looser. In addition to blood vessels, the wall contained several very small, widened ducts, or tubules, lined with epithelium, some of which opened into the cavity. On the outer surface of the connective tissue layer small strands of pancreatic tissue were loosely connected with the wall of the cystic pouch by thin fibers of connective tissue. Also, strands of pancreatic tissue were embedded in the wall of the cyst near the outer surface (fig. 1 and 2). The portion of the duodenum with the papilla of Vater showed two ducts, both patent. One of them contained brown particles (common bile duct), precluding the possibility that the cyst was of the retention type.

The histologic structure of the pancreas was normal; nowhere were distended acini or ducts to be seen. The connective tissue had not increased. Parts of the islets of Langerhans were rather large, a condition which is of normal occurrence in the newborn, as is their relative frequency.

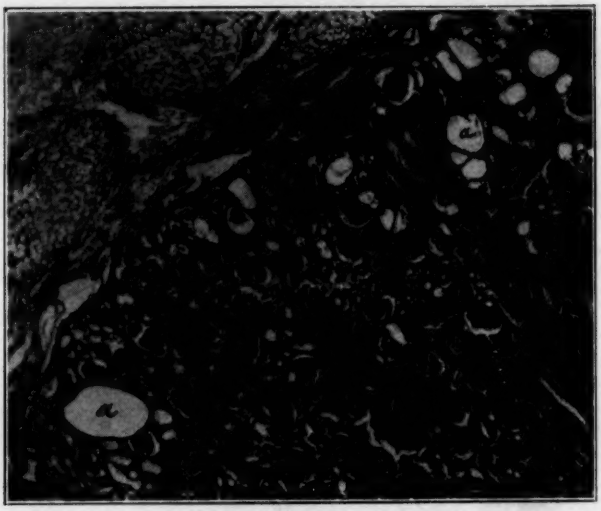

Fig. 3.—Photomicrograph of tissue from kidney, showing the enlarged tubules, *(a)* of cystic appearance, lined with flat epithelium.

The capillaries of the liver were fairly wide and did not contain a surplus of nucleated cells. The same forms of large lymphocytes were seen as had been noted in the blood. The Kupffer cells were not swollen. The parenchyma showed fatty degeneration to a slight degree. Only a few of the smaller bile ducts contained bile thrombi. There were no hemopoietic foci in the sinusoids. This observation was somewhat unusual, as the liver of the newborn infant, especially that of the premature child, practically always contains a moderate number of these foci. Their absence may be explained by the fact that the child was 1 week old when she died; from our own experience, these foci may soon disappear. The connective tissue of the portal canals had increased slightly. In several of them, and about some of the other vessels, there was a slight conglomeration of cells, partly small ones with a dark nucleus and partly fairly large ones with a leptrochromic nucleus. These may have represented foci of erythromyelopoiesis.

In general, the appearance of the kidneys was normal, but a moderate number of tubules contained a homogeneous secretion; near the capsule there were several widened tubules of a cystic appearance lined with flat epithelium. No evidence of nephritis was present (fig. 3).

The adrenal glands were normal. In the unstained sections of the spleen, a considerable number of small malpighian bodies were apparent to the naked eye. On microscopic examination they proved to be without germinal centers. The pulp was hyperemic; the sinuses were fairly wide, and the sinal endothelium was not swollen. The right ovary seemed normal at autopsy and was not removed for examination. In the left ovary the graafian follicles were rather large; some of them could be seen with the naked eye.

In the thymus a differentiation between cortex and medulla was not apparent. Hassall corpuscles were numerous and varied in size. Several showed the concentric ring structure, but many had degenerated. There were also many eosinophilic cells, but they were not abundant, as they should have been, according to Cooper,[1] at the age of this premature infant.

The upper lobe of the left lung was interspersed with small abscesses containing conglomerations of bacteria, of which some were short rods (Escherichia coli?) and some were cocci. In several spots there were traces of meconium. The presence of a purulent bronchitis was observed. The upper lobe of the right lung showed a milder degree of the same process of abscess formation; there was also an extensive lobular pneumonia. The lower lobe of the right lung contained foci of lobular pneumonia. The lower lobe of the left lung showed extensive lobular pneumonia with purulent bronchitis. In all the parts of the lungs examined the pleura was intact.

In summary, in the present case the following developmental errors occurred: (1) large, solitary embryonic cyst of the pancreas; (2) cystic widening of renal tubules; (3) presence of two lobes in the right lung; (4) dystopia ani anterior; (5) polydactyly, and (6) congenital enlargement of the cisterna magna cerebri.

COMMENT

In addition to these anomalies, there was an inflammatory process in the lungs. The question arises whether this was an aspiration pneumonia or an aerogenic infection. In the former, the pleura is seldom attacked; thus, the absence of involvement of the pleura in our case renders probable the diagnosis of an aspiration pneumonia. Moreover, the child was a premature infant, and so especially liable to pneumonia from aspiration. The inflammatory processes in the lungs must be regarded as the cause of death.

According to the classification of Mahorner and Mattson,[2] the following conditions must be considered in differential diagnosis: (1) pancreatic cysts resulting from defective development (cysts in infants, cysts associated with polycystic disease of the kidney, dermoid cysts, inclusion cysts); (2) cysts resulting from trauma; (3) retention cysts; (4) neoplastic cysts, and (5) cysts resulting from parasites. Perhaps it is better to designate only the first and the fourth categories as cysts and the others as pseudocysts.

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2. Webb-Johnson, A. E., and Muir, E. G.: Cysts in the Region of the Pancreas, with Notes of a Case, abstracted, Am. J. Dis. Child. **51**:1187 (May) 1936.

Wegelin[3] stated the opinion that retention cysts cannot be produced by an accumulation of secretion, since this gives only an equal widening of the ductus and its major branches, but that dysontogenetic retention cysts may be due to a developmental error.

In a remarkable number of the cases of traumatic pseudocyst which have been reported, a street accident is mentioned as the causal factor. In several such cases surgical intervention has been successful. In the literature, one also encounters rare cases in which a real cyst, probably the product of a developmental disorder, has been removed from an infant and the child has recovered. In general, in these cases there is no mention of a microscopic examination of the wall of the cyst or of chemical analysis of the fluid it contained; moreover, whether any of these infants presented other congenital anomalies was not stated. Bikoff[4] gave more particulars in his case of an embryonic cyst of the stomach in a girl 26 months of age, which he regarded as an obstruction cyst of the main duct of an accessory pancreas (Wegelin[3]). The cyst was the size of a hen's egg, and by compression it had caused symptoms of pyloric stenosis. Operation was followed by recovery. Microscopic examination of the wall of the cyst showed glandlike spaces deep in the stroma. Bikoff was inclined to regard the spaces as cystic dilatations of branching pancreatic ducts. There were also symptoms of a subacute inflammation. The fluid was not kept for examination. Some doubt may be entertained as to the pancreatic origin of the cyst.

Eha[5] gave the history of a 5 month old child who was born one month prematurely. In the left hypochondrium a mobile tumor the size of a small orange was palpable. A roentgenogram revealed a filling defect of 4 cm. in the descending colon, just distal to the splenic curvature. During the roentgenologic exposure the patient was lying on the abdomen and the tumor displaced the opaque enema, but when the patient turned over the enema passed farther along in the colon and the filling defect disappeared. After incision the tumor was removed. With great satisfaction, the surgeon told us that the child nursed two hours after the operation and during the uneventful recovery never missed a single feeding. The tumor proved to be attached to the tail of the pancreas and consisted of two sacs, a smaller and a larger one, separated by a firm wall. The specimen weighed 99 Gm. The outer wall was firm, smooth and easily indented; the vessels stood out distinctly. The inner lining was smooth; the contents were clear, yellowish, watery and alkaline. Histologic examination revealed fibrous tissue

3. Wegelin, C.: Verhandl. d. deutsch. path. Gesellsch. **18**:169, 1921.

4. Bikoff, H. S.: Embryonal Cyst of Wall of Stomach: Report of Case in Which Symptoms of Pyloric Obstruction Occurred, Am. J. Dis. Child. **56**:594 (Sept.) 1938.

5. Eha, C. E.: Congenital Pancreatic Cyst, J.A.M.A. **78**:1294 (April 29) 1922.

only; there was no infiltration with cells and no lining epithelium. The latter is a curious observation if the author's diagnosis of congenital cyst, rather than pseudocyst, is correct. No analysis was made for enzymes.

The original article of Raghavan[6] was not available. It concerned a child, 3½ years of age who had a slowly growing tumor in the abdomen. Operation revealed a cyst between the stomach and the transverse colon. After incision it was seen to be fixed to the posterior abdominal wall. Its fluid contents were the color of coffee. This coloration led to the conclusion that a hemorrhage, not of recent origin, had occurred into the sac. No details were given as to the relation of the sac to the pancreas. The patient recovered.

Polycystosis of the pancreas is sometimes accompanied with cysts in the kidneys and in the liver, all of which are congenital anomalies. From his own cases and from the literature, Rumler[7] stated that in 5 cases he found the simultaneous occurrence of polycystic pancreatitis with anomalies of the brain and eyes (encephalocele, cerebellar angioma, angioma of the retina and cyst of the lower eyelid). In 1 of his cases there was also polydactyly.

In our patient there is apparently no relation of the origins of the various anomalies. The literature gives such meager information that the possibility of ascertaining whether there were so-called *Koppelmissbildungen* is precluded. One can only say that the period of determination must be placed at an early stage of fetal life.

CONCLUSION

From the study of the literature and our own case, the following conclusions may be arrived at. If a child presents symptoms of vomiting, obstipation and pain, the last symptom usually is fits, and if, moreover, a mobile tumor is felt in the abdomen, there are several possibilities to be considered, such as cyst of the pancreas, ovary or mesentery or hydronephrosis. A roentgenogram, especially a fluoroscopic study after an opaque meal, may be of great use in localizing the site of the tumor. In the literature available we could find a picture only in Caffey's[8] "Pediatric X-Ray Diagnosis." If, after opening the abdomen, one observes a bluish gray tumor, the diagnosis of a cyst becomes almost certain. The surgeon has to take care that no fluid

6. Raghavan, A. K.: Indian M. Gaz. **59**:29, 1924.

7. Rumler, E.: Virchows Arch. f. path. Anat. **292**:151, 1934.

8. Caffey, J.: Pediatric X-Ray Diagnosis: A Textbook for Students and Practioners of Pediatrics, Surgery and Radiology, Chicago, The Year Book Publishers, Inc., 1945. pp. ?

escapes from the cyst into the abdominal cavity, for should it be a pancreatic cyst fat necrosis would result. In the pancreatic cyst, the fluid is clear and yellow; an investigation as to whether it contains enzymes makes the diagnosis certain. As to the microscopic picture of the wall, the small pores on the smooth inner surface, which represent glandlike and ductlike formations, may be of importance in making the diagnosis, as they are not seen in other abdominal cysts.

According to the cases mentioned in the literature, in which a congenital pancreatic cyst was successfully removed or drained, symptoms may be lacking in the beginning, though a tumor is palpable. Only its increasing size with pressure on neighboring organs gives rise to vomiting, constipation and pain. As long as no severe symptoms are present, one is justified in postponing the operation until the child is in fairly good condition and its weight exceeds 3,000 Gm. If other congenital anomalies are present incompatible with life, then in general the surgeon is right in refusing to perform the operation.

In our case, if the surgeon had been willing to operate, even though the infant's weight was only 2,000 Gm., the presence of pneumonia in this premature child would have destroyed all chance of success. Moreover, had the child not died, contrary to all expectation, the development of hydrocephalus probably would have been the result of the malformation of the cisterna magna. There may be cases, however, in which the child's life can be saved.

In the present case, only a roentgenogram of the abdomen was possible; the miserable state of the infant forbade all but the most necessary handling, so that fluoroscopic studies were not feasible.

SUMMARY

The case of a premature child with a large solitary cyst of the pancreas and several other developmental errors is reported. The child died when 1 week old. Autopsy and a microscopic study of the cyst and of the thoracic and abdominal organs were performed and the observations compared with similar observations in the literature.

The patient's chances for recovery had an operation been performed are also discussed

GARGOYLISM (LIPOCHONDRODYSTROPHY)

A Review of Clinical Observations in Eighteen Cases

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SYNONYMS for this uncommon entity are Hurler's syndrome, lipochondrodystrophy and dysostosis multiplex. Gargoylism is the most commonly used descriptive term, although lipochondrodystrophy (Washington's term) is used by the *Quarterly Cumulative Index Medicus*.

It is our purpose in this report to describe the clinical, laboratory and roentgenographic manifestations seen in 16 patients with gargoylism observed during a seventeen year period. On 8 of these 16 patients autopsy was performed. The pathologic lesions observed will be reported at a later date in this journal; they indicate that gargoylism may result from a disorder in carbohydrate storage.

Gargoylism is a disease involving most of the tissues of the body. The skeleton is greatly altered and may be the earliest site of the clinical manifestations. The disease is usually characterized by the following signs: typical facies (like a gargoyle), resembling that of cretinism; cloudy corneas; skeletal changes in both bone and cartilage; dwarfism; infantilism; thickening of the skin and periarticular structures limiting extension of joints; hepatosplenomegaly, and mental retardation. There is occasional familial recurrence, but no predilection as to sex or race has been noted.

HISTORICAL OBSERVATIONS

Hunter, in England, first described this disease in 1917 and stressed the skeletal involvement. Hurler, in Germany, then added the observations of mental retardation and cloudy corneas in 1919. Helmholz and Harrington wrote the first report of the syndrome in the American literature. Observations at the first autopsy were reported in 1934 by Tuthill, who described the storage in the brain of a lipid resembling cerebrophosphatid. Lipid was not seen in the skeleton at the other

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autopsies reported by Reilly (1935), Ashby and associates, Kressler and Aegerter, Kny and de Lange and associates (1944). Strauss and associates, Schmidt and Strauss, in their reports of fatal cases, contended that there was an excess of a lipid in the involved tissues. The term gargoylism was applied in 1936 by Ellis, Sheldon and Capon, in England. At present, owing to the gaps in knowledge, we prefer gargoylism as the descriptive term for the disease. About 107 case reports were found and verified after a thorough search of the literature to January 1947. There are a number of good reviews on the subject (Bocker, Boldt, Engel, Halperin and Curtis, Henderson, Kressler and Aegerter, Strauss and associates, Veasey, and Washington).

ETIOLOGIC ASPECTS

The appearance of clinical signs in infants as young as 2 months of age (kyphosis), the familial recurrence in 5 of 13 of the families in the present study and the altered skeletal growth would indicate a hereditary defect of the germ plasm. A similar thesis has been entertained to explain achondroplasia. Likewise, the storage phenomenon in the tissues, possibly of carbohydrate type, could be regarded as a constitutional metabolic disorder. We feel that there is storage of some material in the parenchymal cells of the body. This material is not lipid in nature and may be a carbohydrate. In tissues obtained from 8 patients at autopsy, the amount of fat in the involved tissue cells was no greater than normal. Macromolecular substances, such as acacia, glycogen, methyl cellulose or polyvinyl alcohol, after repeated intravenous injections, are deposited in the parenchymal cells of many tissues, with resulting histologic changes resembling those of gargoylism (Hueper). In rabbits receiving injections of the macromolecular carbohydrate methyl cellulose for several months, there were changes in the viscera resembling those of gargoylism; in 3 of 22 animals there developed corneal opacities similar to those seen in gargoylism (Lindsay).

The manifestations of the disease in the skin, skeleton and face which suggest disease of the thyroid gland or pituitary body are probably due mainly to storage of the material in the involved structures and partly to an endocrine dysfunction, since the storage phenomenon also occurs in these, and other, endocrine glands.

The histories of 5 of 13 families showed recurrences in the same generation. One family had double ovum twin girls, 1 of whom was afflicted. The other twin is now 18 years of age and is free from this disease. A second family had 2 boys with gargoylism; the younger boy had a normal twin sister. The third family had 2 affected brothers, and the fourth and fifth families each had a brother and a sister with the disease. A familial congenital constitutional defect of the germ plasm

seems likely in gargoylism. Bocker cited 3 cases with familial recurrence. In 1 family, 20 of 53 children in three generations were stillborn or died during infancy. In the last generation, there were 7 children in 1 family, and, of these, 1 had dysostosis multiplex and 2 had Morquio's disease (eccentro-osteochondrodysplasia). In another family, of 11 children, there were 2 girls with dysostosis multiplex and 2 boys with Morquio's disease. In the third cited instance, in the line of descent from 1 woman, there were 1 boy with dysostosis multiple in the second

Fig. 1.—A boy, aged 3½ years, and a girl, aged 12 years, with gargoylism. Note the similar facial appearance, the hirsutism, the protruding abdomen with umbilical hernia and hepatosplenomegaly and the skeletal deformity with dwarfing and crouched stance.

generation, 1 girl with Morquio's disease and 2 boys with dysostosis in the third generation and 1 boy with dysostosis in the fourth generation.

Halperin and Curtis discussed the genetics and familial recurrence of gargoylism.

SIGNS AND SYMPTOMS

The appearance of a child with gargoylism (fig. 1) is so typical as to be unmistakable. All persons with this disease have such a remark-

able resemblance to one another that familial relationship is strongly suggested. So gruesome is the appearance that the exaggerated descriptive term gargoylism was applied by Ellis and associates. The thickened features, narrowed palpebral fissures, sunken nasal bridge, open mouth, protruding thick tongue, and large skull developed at 1 to 1½ years of age in most of our patients. In 1 child the typical facies was present at 3 months of age. However, 2 patients did not show facial changes at 2 and 4½ years of age, respectively. The skull enlarged soon after birth and was dolichocephalic in 14 children and scaphocephalic in 1 child. All our patients had fairly pronounced skeletal changes, including short stature, short thick neck, with the head appearing to arise from the chest, kyphosis and the inability to extend the joints fully. They stood partly crouched, with the thighs partially flexed and abducted, the knees in genu valgum and the feet everted. In many patients, the long bones were thickened and deformed at their ends, and the hands were occasionally in a position of ulnar deviation, owing to the obliquity of the lower radial epiphysis. The small joints of the wide, stubby hands and feet were partially flexed, giving the fingers and toes a clawed appearance. The changes in the hands and feet were apparent in all 16 patients, most of them having this deformity by 6 to 12 months of age. The trunk appeared shortened in all. Kyphosis, limited to the thoracolumbar juncture, was seen in 12 of 14 patients. It appeared as early as 2 months of age in 1 patient, at 3 months in another and by the age of 6 months in 3 others. A long, smooth dorsal curvature was present in 3 of them and a lordosis (with a roentgenographic vertebral defect) in the remaining 4. The kyphosis was movable.

Analysis of our patients indicates that kyphosis is the earliest abnormal sign, appearing months before the hepatosplenomegaly or the facial and corneal changes. Increased obtuseness of the angles of the mandible, with short rami, was present in most patients. This malformation caused biting defects of the anterior teeth. Peg-shaped, widely spaced teeth were present in 9 of 11 patients so examined. The neck was short, wide and limited in motion, and the large head seemed to rest directly on the top of the thorax. The limbs of our patients were disproportionately short. The liver and spleen gradually enlarged, so as to be palpable as early as 8 months of age, or by the age of 1 year in most of our patients. In only 1 patient were these organs not palpable. The skin was thickened and lardaceous and lacked subcutaneous elasticity, particularly on the forehead, face, shoulders, axillas and the dorsum of the forearms and hands. One patient had multiple small, aggregated nodules in the axillas, due to subcutaneous fibrosis without scleroderma or myxedema. Biopsy of other nodules showed mild, chronic nonspecific dermatitis. The changes in the skin appeared as early as 6

months of age in 1 patient and were present by 1 or 1½ years of age in 4 others. No changes in the skin had appeared, however, at later ages in 5 of 10 patients so examined. Three patients had eczematoid dermatitis of the face. The external ears were usually softer and less elastic than normal. The small, deformed thorax displaced the liver and spleen downward from their normal positions. These viscera also underwent enlargement and increased density but were usually smooth. Cloudiness of the corneas, which is not found in other storage diseases, was seen in 14 of 16 patients. The condition was evident by the age of 1 or 2 years, though 1 patient did not have such an alteration in the corneas at the age of 10 years. Corneal cloudiness is due to storage in the deeper layers of the cornea, and it is better seen with a slit-lamp, by means of which the material appears as myriads of small, refractile particles. A detailed report of corneal changes in a number of our patients was made by Cordes and Hogan. The infiltration caused near blindness in 4 patients and progressively diminishing vision in the others. The eyes appeared protuberant or bulging, but the intraocular tension was not raised. Occasionally, there was convergent strabismus; 1 patient had a pupillary membrane, and 1 had papillary edema. A reduction in hearing ability was a complaint of 9 of 12 patients so examined. One child was totally deaf. The hearing deficiency usually began by the age of 6 to 12 months. Chronic nasal infection with profuse discharge and noisy oral breathing was an early complaint in the majority of cases. Some of the patients had constant nasal infection, and this complaint often antedated kyphosis. While frequent infections of the respiratory tract with enlarged adenoids could account for some of the loss of hearing, the examining otologists also occasionally suspected lesions of the eighth nerve.

Of 16 patients whose records noted the condition of the umbilicus, 12 had umbilical hernia. It was first noted clinically at birth (1 patient) and at the ages of 1 month (1 patient), 1 year (5 patients), 2 years (2 patients) and 4½ years (1 patient). Some of these hernias were extremely large. Several male patients had inguinal hernias as well. Hirsutism of the eyebrows, scalp, neck, extremities and back was noted in 8 of 14 patients. It was first found clinically at the ages of 1, 2, 3 and 5 years (1 patient each). In 1 child 6 years of age a small amount of pubic hair was present. No other unusual sexual characteristics accompanied this hirsutism, although 1 patient had mild clitoral hypertrophy. The clinical cardiac signs particularly interested us in view of our pathologic observations of narrowed, thickened coronary arteries and thickened cardiac valves. Of the 16 patients, 9 had no cardiac signs or symptoms. Of these 9 children, 1 also had a normal cardiac roentgenogram; electrocardiograms were made for 2 of these patients: for 1 the record was normal, and for the other it showed auricular extrasystoles. The clinical

findings in the other 7 patients consisted chiefly in systolic murmurs along the left sternal border. In 3 of the 7 children a defect of the intraventricular septum was suspected. One child was thought to have pulmonary stenosis. One of the 3 children with suspected congenital cardiac defects had a normal electrocardiogram. Of 3 other patients of the 7 with systolic murmurs, 1 had the murmur at 8 months of age; another had it when 3 years old, with cardiac decompensation appearing at 7½ years and a diastolic apical murmur at 10 years of age. At this time an enlarged aortic root was also detected. The third patient seemed normal at 7 years of age, but the systolic murmur became audible when the patient was 8 years of age, and he died of cardiac decompensation at 11 years.

Of the children whose intelligence was measured (15 patients), all but 3 were mentally retarded. As the 2 surviving patients with normal intelligence live on, we expect a lowering of the intelligence quotient, although they have been under observation two and four years, respectively. The third child was exceptionally intelligent, and pathologically his brain showed minimal changes. The disease appeared at the age of 6 months, and he died at the age of 11 years. Early in life he became almost totally deaf. At the age of 8¼ years, his mental age was 9 3/4 years; he learned spontaneously to read lips at the age of 5 years. His speech was limited to a few words. In the rest of the children progressive mental deficiency developed from six months to one and a half years after the clinical onset of the disease.

The clinical signs, as well as roentgenographic changes, vary with the age at onset, the frequency of occurrence and the degree of involvement of various tissues. In general, the older the patient, the more profound are the changes and the more likely are all of them to be present. In our patients chronic infections of the respiratory tract, kyphosis, facial changes and hepatosplenomegaly had started at the age of 6 months to 1 year. These signs were soon followed by limited extension of joints, cloudy corneas, hepatosplenomegaly and mental retardation. The signs in the latter group were not detected until the patients were about 2 to 3 years of age.

LABORATORY DATA

Studies of the blood showed an occasional case of mild hypochromic anemia and leukopenia in about half of the patients. In half of the patients a peculiar granulation was present in 60 to 90 per cent of the polymorphonuclear leukocytes. These granules, as reported by Reilly (1941), are usually large, uniform and numerous, and they take a dark lilac stain with the Giemsa-Wright technic. These granules do not resemble toxic granules. We have seen them in puncture biopsy speci-

mens of the spleen and bone marrow. Lipid analysis of the blood of 5 patients was made. In only 1 child did the results suggest a fat storage process in that the total cholesterol (250 to 387 mg. per hundred cubic centimeters), the total lipids and the total fatty acids were elevated in several tests (respective values were 1,060 and 642 mg. per hundred cubic centimeters). High and low fat diets given to 2 patients did not alter the normal blood fat values. Phospholipid levels of the blood were also normal. Kerasin, phrenosin and cerebrosides were not detected in the blood of 1 patient so tested. Some, or all, of the following tests were made on the blood of each patient at various stages of the disease: determinations of calcium, phosphorus, alkaline phosphatase, and urea nitrogen levels, icteric index, sulfobromophthalein retention and sedimentation rate; the van den Bergh test; the oral and intravenous dextrose tolerance test, and the oral galactose test. The tests were repeated, with normal results, in 8 patients. Epinephrine tolerance was normal in the 1 patient tested. In 1 patient a hippuric acid test gave abnormal results. This reaction was the only evidence of abnormal hepatic function we found by laboratory methods. The Wassermann reactions of 14 patients were negative. The Wassermann test is a helpful procedure, since the general appearance, facies, corneal alterations, abnormal teeth and hepatosplenomegaly had led to antisyphilitic therapy of several of these patients. Urinalysis showed nothing abnormal for 17 patients. Encephalograms were made for 2 patients; 1 showed frontal atrophy, and 1 showed uniform ventricular dilatation.

ROENTGENOGRAPHIC FINDINGS

In a typical severe case the roentgenographic diagnosis is often most characteristic (fig. 2). Sometimes the skeletal changes are the most helpful single diagnostic finding. They may be poorly developed in some cases which are otherwise typical, but with time they become more pronounced.

Configuration of the skull is unusual. It is usually dolichocephalic, that is, considerably longer in its anterior-posterior diameter than in its width, with its greater width in the temporal region. The frontal areas overlie the orbits anteriorly to a considerable degree. The sella turcica is greatly elongated in its anterior-posterior dimension, and it is shallow. The clinoid processes often are poorly developed and stand upright. They are not eroded. Often there are numerous convolutional markings on the inner table of the skull. The maxilla and, in many patients, the ascending mandibular rami are underdeveloped. The mandibular angles are greatly increased. As a result, there is a forward protrusion of the mandible with an overbite of the lower incisor teeth, so that biting is not satisfactory. In 1 of our older patients (12 years of age) absorption

of bone was noted about the molars, giving the appearance of bilateral dentigerous cysts.

The scapulas, in many patients, are widened. The ribs have narrow roots and broad bodies, with necks which appear distorted. Often they

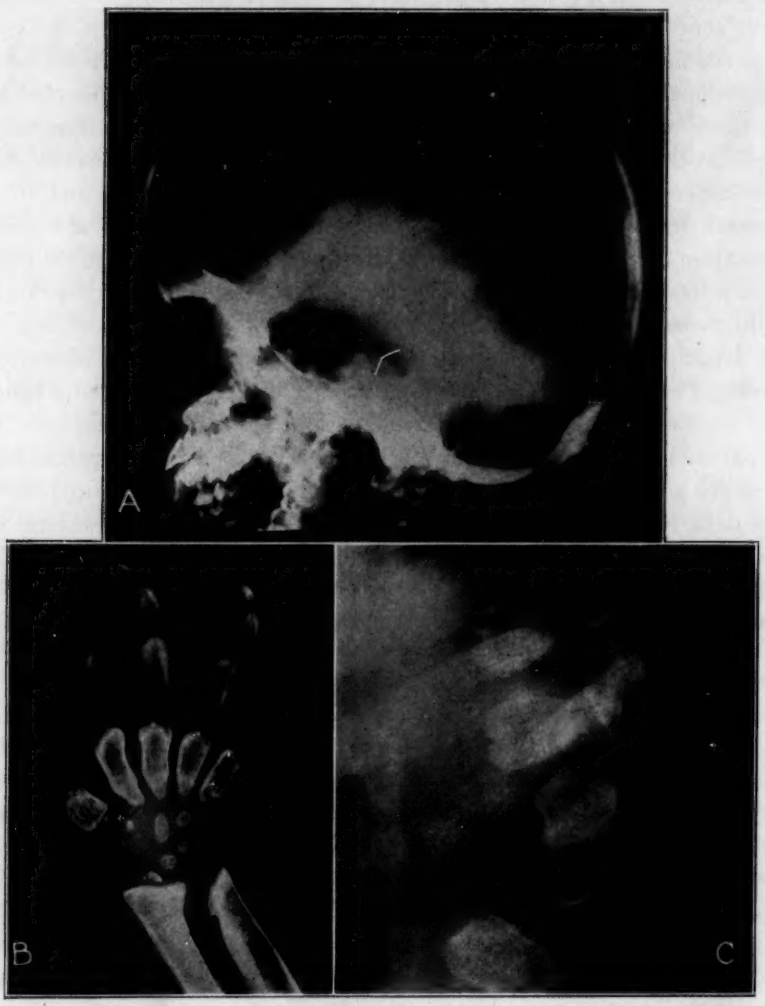

Fig. 2.—The principal skeletal changes in persons with gargoylism as seen on roentgenograms. *A*, the irregular vault of the skull and the greatly enlarged, shallow sella turcica; *B*, the obliquity of the lower articular surfaces of the radius and ulna and the broadened, irregular metacarpal bones and phalanges, and *C*, the anterior notching of the irregular vertebral bodies in the upper part of the lumbar portion of the spine.

leave the spinal column at almost a right angle. The clavicles are distorted and wide. The superior halves of some of the vertebral bodies (between the twelfth thoracic and the second lumbar level) do not ossify at the same rate as the inferior halves, so that there is a steplike

formation in the anterior surfaces of these bodies, resulting in the kyphosis so often noted clinically. A long, smooth dorsal curvature of the entire spine is occasionally seen. In 2 cases we found kyphosis developing later in life in the cervical portion of the spine as well.

In the extremities the magnitude of changes varies greatly; but these changes are more pronounced in the upper than in the lower extremities, and the upper extremities are invariably affected. Characteristically, there are decided retardation of epiphysial maturation, abnormal configuration of the shafts and irregular cartilagenous proliferation at the epiphyses. The shafts are short and stubby and exhibit bizarre swellings in the central portions, which taper toward the ends; the latter feature is a significant diagnostic sign. In the upper extremities, the head of the humerus is thick and exhibits a valgus angulation. The articular surfaces and the epiphysial plates of the lower ends of the radius and ulna face inward. Occasionally, only one of the two bones shows this change. The metacarpal bones, the proximal portions of the metatarsal bones and the phalanges are broad and shortened, and the first two phalangeal bones are pointed at their ends. In the lower extremities, both acetabulums are shallow, and the ischia are disproportionately small in relation to the ilia. The femurs show a coxa valga angulation of the neck and a malformed, flat appearance of the head. The necks are broad. Invariably, genu valgum is present, owing to the tilted epiphyses and lines of femurs and tibias. The feet show the same characteristics as those described in the hands. The epiphysial plates of the long bone are usually flat and deformed, and they often have irregular outlines of ossification. Occasionally, there is a fragmentation in the ossification process. Retarded epiphysial age was observed in about one-half the patients, especially in the older children. This retardation amounts to two to four years.

In all our patients, kyphosis was found roentgenographically and in all except 2 clinically. As mentioned previously, the epiphysial age lags, becoming more pronounced in the older child. The lag is not so great as in hypothyroidism. In 3 of our patients the only definite finding was that on the roentgenogram. These 3 patients were young children whose other bodily characteristics had not developed enough to make physical diagnosis certain. We regard kyphosis in an infant as a suspicious sign of gargoylism, especially if tuberculosis and other common causes of the condition are ruled out.

In Morquio's disease one finds suggestions of chondrodystrophy in that the ends of the shafts flare widely and overhang the growing plates; the reverse is true in Hurler's syndrome. In the latter condition the shafts are much thicker in their central portions and taper toward the ends. In Morquio's disease there is a tendency to thin cortices and osteoporosis; the epiphyses are more deformed or fragmented.

DIAGNOSIS

Gargoylism will be readily recognized by any one having once seen a patient with the disease. The typical facies, cloudy corneas, dull expression and mentality, the crouched stance and genu valgum, the thickening of the skin and periarticular structures, limiting extension of joints, thoracolumbar kyphosis, hepatosplenomegaly, familial recurrence and the osteochondrodystrophy seen on the roentgenogram are not combined in any other disease. The retarded mentality and cloudy corneas are not always present in the young patient; familial recurrence may not be observed. In our group, skeletal changes, especially kyphosis, were the earliest sign, appearing as early as 2 months of age in several patients and by 6 months of age in 5 others. By the age of 12 to 18 months, the changes in the facies, the hepatosplenomegaly, the retarded mentality and, to a less extent, the cloudy corneas were clinically recognizable in most of them. In Morquio's osteochondrodystrophy, the length of the trunk remains normal, the cornea of the skin does not change, the spleen and liver are not enlarged, the mentality usually is unimpaired and no such gruesome facies occurs. We wonder whether Morquio's disease is essentially the skeletal form of gargoylism, so similar are the roentgenologic appearances. To date there have been few adequate descriptions of the pathologic features of Morquio's disease. A biopsy reported by Shelling showed changes similar to the osseous lesions in our cases of gargoylism. In the report of Einhorn and associates, the description of the pathologic lesions of bone in Morquio's disease resembles the picture in gargoylism. In hypothyroidism cloudy corneas do not develop, and hepatosplenomegaly and familial recurrence are rare. The pathologic changes are dissimilar to those of gargoylism. The response of patients with gargoylism to thyroid is limited. In congenital syphillis, the corneal changes never include the deep-seated, highly refractile granules; the reaction to the Wassermann test in gargoylism is negative, and antisyphilitic therapy does not result in improvement or cure. Persons with gargoylism resemble those with hypertelorism in that their eyes are separated more than normally. Patients with hypertelorism never show cloudy corneas, hepatosplenomegaly or changes in the long bones.

PROGNOSIS

Persons afflicted with gargoylism usually die before their eighteenth year, and the great majority are dead by the age of 10 or 12 years. As exceptions, the patient of Strauss and associates lived to the age of 23 years, that of de Lange and associates (1944) until 18 years of age, and Sawyer's patient was reported to be alive at 19 years of age. The ages,

in years, at the death of our 8 patients were 11, 8, 7, 4, 3, 6½, 5 and 1. Cardiac decompensation, primary tuberculosis with pneumonia and bronchopneumonia, in 2 cases, were the immediate causes of death.

TREATMENT

We know of nothing that will help these children. Certainly, endocrine products are of no great value, though occasionally thyroid seemed to improve the sluggishness, the dryness of hair and skin and the constipation. Symptomatic therapy is indicated, even if given only as a placebo. The kyphosis can be helped by use of the Bradford frame; light braces may be used for the genu valgum, with the possibility of osteotomy at a later date. Corrective shoes may be indicated for the everted feet. Institutionalization should be urged for children with the greater degrees of mental deficiency, especially if normal siblings are made to suffer psychologically, financially or in other ways, or if the patient becomes an object of curiosity. Families should be warned that the disease not infrequently may recur in future offspring.

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Obituaries

FRANK C. NEFF, M.D.

1872-1947

The death of Dr. Frank Chaffee Neff, Dec. 3, 1947, brought to an end a long, full life of pediatric practice and teaching. Dr. Neff died of coronary artery disease at the University of Kansas Medical Center, where he headed the department of pediatrics from 1924 until his retirement in 1946.

He was born in Winchester, Ind., Aug. 1, 1872. He attended the University of Iowa and was graduated from the University Medical College of Kansas City, Mo., in 1897. After his internship he spent one year at the New York Infant Asylum and two years at the Kings County Hospital in Brooklyn. After eight years of general practice he took postgraduate training in Berlin, Germany, in 1910, returning to the United States to devote his full time to pediatrics. He was married to Helen Josephine Cole of Knoxville, Tenn., in 1902, who, with his three children, survives him.

Dr. Neff's endless store of energy and his intense interest in clinical pediatrics that never waned until he was stricken with his last illness always astonished his younger colleagues. He never met a class of medical students without preparing for the session, although he was an avid reader; through the years he constantly labored to enrich his profound store of knowledge in the field of child health. In sharing his experience in ward rounds with students and members of the house staff, and with his colleagues in his frequent attendance at medical meetings, he made a contribution to the advancement of pediatrics in his section of the country that cannot be overestimated.

Dr. Neff contributed approximately 66 articles to the medical literature, as well as chapters on scurvey and rickets to Abt's "Pediatrics," Tice's "Practice of Medicine," Piersol's "Cyclopedia of Medicine" and Clendening and Hashinger's "Methods of Treatment" and a monograph on "Diseases of the Digestive System in Childhood" in Appleton's clinical pediatrics series.

He found relaxation in good music and in his garden. Few physicians enjoyed medical meetings more than he did. He participated in the organizational work and the scientific sessions with a devotion to the advancement of medicine that endeared him to his pediatric colleagues.

He served as chairman of the Section on Diseases of Children of the American Medical Association in 1920-1921, at which time he proposed the creation of the Abraham Jacobi Memorial Fund. He was a charter member of the Central States Pediatric Society and never missed a meeting during the fifteen years of its existence. He was also a charter member of the American Academy of Pediatrics, and in 1923 he was elected to the American Pediatric Society. Twice he attended the International Congress of Pediatrics, at Stockholm, Sweden, and at London, England.

Frank Neff was a great moral force in his community, a man who saw none of the frailties of his associates, one devoted to his family and generous with his time and his resources to every worthy cause. His passing marks the end of an era in the professional lives of those who were privileged to come under his influence.

H. L. D.

News and Comment

GENERAL NEWS

Physicians Certified by the American Board of Pediatrics.—The following physicians were certified as specialists by the American Board of Pediatrics after examinations held at Cleveland, April 23, 24 and 25, 1948:

Alfred B. Amler, White Plains, N. Y.; Raymond Burk Anderson, Kansas City, Mo.; Emanuel Berger, Philadelphia; Abraham Berkow, Hackensack, N. J.; Benjamin Clemens Berlinger, Hewlett Harbor, N. Y.; Joseph Bitman, Philadelphia; Louis Clair Burket, Altoona, Pa.; Henry Burkhardt, Holyoke, Mass.; Nathan Cabot, Bronx, N. Y.; Harold Arthur Cassady, Cincinnati; Mary Clark, Hattiesburg, Miss.; Elizabeth Conrad, Winston-Salem, N. C.; Douglas Stanton Damrosch, New York; William Dwight DeVaux, Cincinnati; Ernst H. Dreyfuss, Chicago; Albert M. Edmonds, Elizabeth, N. J.; Jackson K. Eto, St. Louis; Abraham Gilner, Brooklyn; M. Elizabeth Grant, Cambridge, N. Y.; Helen Hardenbergh, San Jose, Calif.; Charles Hilliard Hollis, Lawrence, Mass.; Edwin Lawrence Kendig, Jr., Richmond, Va.; Eva Landsberg, New York; Carolyn Moore McCue, Richmond, Va.; Ethel Mae Madden, Columbia, S. C.; Noah Miller, Akron, Ohio; William J. Morrow, Ann Arbor, Mich.; Edward J. Muldoon, Cuyahoga Falls, Ohio; Francis D. Nance, Honolulu, Hawaii; Alice Chassel Nauen, Cambridge, Mass.; William Warren Owens, Brooklyn; Nicholas Elias Pingitore, New York; Marlin H Poindexter, Jr., Fargo, N. D.; Charles Rosenfeld, Philadelphia; Hubert A. Royster, Jr., Bryn Mawr, Pa.; Allan A. Rubenstein, Laurelton, N. Y.; Isaac Hillson Schwartz, New Bedford, Mass.; Benjamin B. Shaver, San Antonio, Texas; Robert Colby Storrs, Hanover, N. H.; Sidney Wachtell, Bronx, N. Y.; Thomas H. Weller, Boston; James Alexander Wolff, Boston.

Abstracts From Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

APPETITE, HUNGER AND OBESITY IN YOUNGSTERS PAST AGE TWELVE. ISRAEL BRAM, Arch. Pediat. **63**:581 (Nov.) 1946.

The author feels that uncomplicated obesity in the youngster is the simplest and easiest of all maladies to cure. He discusses normal and abnormal appetites and the various factors in each as they relate to normal weight and obesity. He then presents his method of weight reduction, which consists in curbing the appetite, the careful formulation of a submaintenance diet and the occasional use of selected drugs.

DAVIS, Denver.

NUTRITIONAL DEFECTS AMONG CHILDREN IN VERMONT. M. B. PIERCE, P. F. FENTON, WALTER WILKINS, M. E. NEWLAND and PAULINE S. BUDGE, New England J. Med. **233**:612 (Nov. 22) 1945.

Inspection for physical signs of nutritional defects and analyses of the blood for vitamin C and hemoglobin content were completed for 176 and 170 respectively of a total of 386 children. In the city children in six classrooms were studied in addition to those in two institutions. The children were classified as follows: group A, those from a high income area; groups B and D, from both low income and high income areas; group C, from a low income area; groups F and G, from rural areas, and groups E and H, those from children's homes. The age range in rural schools and at each of the two institutions was greater than that in the individual grades at the city schools.

A review of the food intake showed as the greatest fault the low intake of fruits and vegetables. Blood studies revealed that 25 per cent of a group of 176 children had vitamin C levels in the plasma below 0.6 mg. per hundred cubic centimeters, and on physical inspection 40 per cent of the entire series had inflammation of the gums of varying intensity. Severe forms of spongy, bleeding gums were seen in only a small percentage of the children. Six per cent of 170 children had low hemoglobin values suggestive of mild anemia. Urban children had higher hemoglobin levels than rural children. Skeletal changes usually associated with rickets were seen in almost 85 per cent of the children. The signs chosen were looked for with extreme care, and even minor deviations were included.

Signs associated with a shortage of riboflavin were also observed in a small percentage of the children, but they cannot be accepted as definitely indicating any serious deficiency of this vitamin. Some degree of folliculosis, at least of the outer aspect of the arm, was seen in 40 per cent of the children, and 5 of these subjects had generalized folliculosis of pronounced degree. Mild cases of follicular conjunctivitis were frequent. Premature loss of teeth and dental caries were exteremely prevalent, being seen even on gross examination with a good light and a tongue depressor.

GENGENBACH, Denver.

MODIFICATION OF FAT ABSORPTION IN CHILDREN WITH ADMINISTRATION OF SODIUM GLYCEROPHOSPHATE. D. VITTORIA BORI and ARMIDA SCHIAFFINO, Riv. di clin. pediat. **40**:661 (Nov.) 1942.

Studies of fat absorption were made on 10 children. The administration of 10 to 20 mg. of sodium glycerophosphate per kilogram of body weight resulted in higher fat absorption in 7 of the children. The percentage of fat in the feces present as neutral fat was lower in each of the children receiving the sodium glycerophosphate.

HIGGINS, Boston.

CURVES FOR CAPILLARY AND VENOUS GLYCEMIA IN HEALTHY AND IN SICK CHILDREN. G. ROBERTO BURIGO, Pediatria **54**:372, 1946.

After discussing the most important clinical and experimental contributions to the study of capillary and venous glycemia and the application of this knowledge to children, the author refers to data contained in 55 curves for glycemia. Twelve of the curves were for normal children, while 43 were for subjects with diseases resulting in various metabolic changes.

The conclusions drawn from the data obtained are as follows: the differential curves for healthy children are at their highest when the hyperglycemia peak of the capillary curve is reached. The curves are similar to those that the majority of authors obtained for healthy adults. For sick children the differential curves are, in relation to the curves for normal children, more or less altered according to the extent of metabolic change caused from the disease. In patients with symptomatic ketosis the value for glycemia in the differential curve is always altered.

FROM THE AUTHOR'S SUMMARY.

Vitamins; Avitaminoses

VITAMIN D METABOLISM: II. A STUDY OF TWO CASES OF HEPATIC RICKETS. RENE HOUET, Ann. paediat. **167**:113 (Sept.) 1946.

In children with congenital atresia of the bile ducts, a clinical syndrome of persistent jaundice, cirrhotic enlargement of the liver and splenomegaly due to colostasis is seen. In these cases the urine is dark brown with many bile salts and bile pigments, while the stools are voluminous, hard, fatty and gray. Rickets may sometimes develop in these children, with rosary, hypophosphatemia, thinning of the cortical epiphysis and enlargement of the ulnar and fibular epiphyses.

Experiments to determine the calcium and phosphorus balance show a poor resorption of both minerals in the intestine, which is worse than the average shown in children with ordinary rickets. The phosphatase values, however, are normal, and the quotient of fecal phosphorus/urinary phosphorus differs from the average obtained in ordinary rickets.

Oral administration of vitamin D is futile because of the lack of absorption as shown by the balance experiments. The feces yielded more than 80 per cent of the ingested vitamin D preparation. The role hepatic damage may play in the pathogenesis of rickets is discussed, as well as the role of a healthy liver in normal metabolism of vitamin D.

FROM THE AUTHOR'S SUMMARY.

DETERMINATION OF VITAMIN B_6 CONTENT OF HUMAN BLOOD, COLOSTRUM AND MILK. A. COLARIZI, Riv. di clin. pediat. **40**:321 (June) 1942.

Recent investigations at the pediatric clinic in Rome, Italy, indicated that desquamative erythroderma in infants (Leiner's disease) is the result of vitamin B_6 deficiency. Hence the author made studies to obtain data on the vitamin B_6 content of the blood, colostrum and milk of nursing and expectant mothers.

The mean vitamin B_6 content of the blood of pregnant women was 12.7 mg. per hundred cubic centimeters (the range was 8.0 to 18.2 mg.), and that of the blood of 22 nursing mothers 14.6 mg. (a range of 10.5 to 18.8 mg.), while the milk of these mothers contained 9.8 mg. (a range of 6.2 to 14.7 mg.). In the colostrum and blood of 8 mothers, the mean amounts of the vitamin were 15.7 and 13.4 mg., respectively. The vitamin B_6 content of the blood and the milk of mothers with low initial values and of the blood of nursing infants increased within twenty-four hours after the injection of 50 mg. of adermin.

Cow's milk is plentifully supplied with vitamin B_6. Pasteurization caused a loss of 25 per cent of the vitamin and boiling a loss of 50 per cent. Milk made from dried whole milk powder was found to contain about 25 per cent less of the vitamin than raw milk. When cows were given fodder containing fresh vegetation, the vitamin B_6 content of the milk increased.

HIGGINS, Boston.

URINARY EXCRETION OF NICOTINIC ACID IN HEALTHY AND SICK CHILDREN. A. BOLLETTINO and E. COSSANDI, Riv. di clin. pediat. **40**:544 (Sept.) 1942.

Observations were made on 10 breast-fed infants, 10 artifically fed infants, 10 older children and 4 adults, all of whom were well, and also on 11 infants with various illnesses, such as rickets, bronchopneumonia and colitis. The normal excretion of nicotinic acid was 0.01 mg. per day for the breast-fed infants, 0.05 mg. for the artificially fed infants, 0.06 for the older children, 0.09 for the adults and 0.02 mg. for the sick children. When 50 mg. of nicotinic acid was fed to the infants, 100 mg. to the children and 150 mg. to the adults, the percentage of the vitamin eliminated over twenty-four hours was 0.09 per cent for the breast-fed infants, 1.4 per cent for the artificially fed infants, 2.93 per cent for the older children, 4.53 per cent for the adults and 0.7 per cent for the sick infants. The excretion was extremely low in infants with colitis.

HIGGINS, Boston.

OSSEOUS TYPE OF INFANTILE SCURVY. A. GALEOTTI FLORI, Riv. di clin. pediat. **40**:641 (Nov.) 1942.

A report is given of a case of scurvy in a girl 3 years of age with severe subperiosteal hemorrhages in the right humerus and the left tibia.

HIGGINS, Boston.

PHARMACOLOGIC STUDIES ON PANTOTHENIC ACID. L. NASSI, Riv. di clin. pediat. **41**:443 (Aug.) 1943.

Observations were made on rabbits, frogs and guinea pigs. Pantothenic acid was found to intensify and prolong the hypertensive action of epinephrine. It slowed the rate of the beat of isolated frog's heart. Since this effect was no longer evident after atropine U.S.P. was used, one may conclude that pantothenic acid acts on the receptors of the vegetative nervous system.

HIGGINS, Boston.

VITAMIN D RESISTANT RICKETS. BERNHARD BESKOW, Nord. med. (Hygiea) **25**:117 (Jan. 19) 1945.

At 4 years of age a girl began to have difficulty in walking. Her legs became crooked, and, when first seen at 5 years of age, she was unable to support herself on them. There were pronounced genu valgum and roentgenographically active rickets. Phosphorus in the blood measured 1.5 mg., calcium 10.6 mg. and phosphatase 17.4 units, per hundred cubic centimeters. The spleen and liver were enlarged. The child was given large doses of vitamin D and 500,000 units in all of vitamin D_2. In addition, ultraviolet treatment was given daily from June to September. The rachitic changes showed only a slight tendency to heal. After three months, the phosphate level in the blood was 1.8 mg., and phosphatase measured 66.8 units per hundred cubic centimeters. In the meantime, the liver became still more enlarged and ascites was demonstrated. The case is believed to be an example of the hepatic rickets of Gerstenberger, which is caused by cirrhosis of the liver of unknown origin.

WALLGREN, Stockholm, Sweden.

Prematurity and Congenital Deformities

TWO CASES OF HYPERTELORISM (GREIG). M. SCHACHTER, Ann. paediat. **167**:199 (Oct.) 1946.

The author describes 2 personal cases of hypertelorism (Greig). The first case was of a child, 5 years of age and represents the pure type. The second was of a 13 year old girl during puberty, who had in addition a unilateral harelip. Both children were mentally defective and had relaxed joints. A short discussion of symptoms and diagnosis is included.

FROM THE AUTHOR'S SUMMARY.

PROTHROMBIN LEVEL IN BLOOD OF PREMATURE INFANTS. J. H. MAGNUSSON, Nord. med. Hygiea) **25**:34 (Jan. 5) 1945.

The prothrombin index in 95 premature infants and, for comparison, in the same number of full term infants was determined during the first four weeks of life. For the first two days after birth the prothrombin index was significantly lower statistically in the premature infants than in the full term children. Later, there was no demonstrable difference, but a certain liability in the regulation of prothrombin production was probable even in the second week of life.

WALLGREN, Stockholm, Sweden.

HUMAN SERUM AS ADDITIONAL FOOD FOR PREMATURE INFANTS. JOHN LIND, Nord. med. (Hygiea) **28**:2461 (Nov. 23) 1945.

The premature infant's increased requirement of calories and protein is often difficult to supply with breast milk alone. The simultaneous inadequacy of digestion and metabolism reduces the possibilities of making up the shortage with additional nutriment. With the inclusion of low molecular, easily resorbed amino acids in the diet, good results and a rapid increase in weight are gained. It has long been known that colostrum is of great value in the feeding of premature infants who are considered capable of utilizing its protein, either without any breakdown of the proteins at all or, at least, without complete splitting of the molecules. The protein substances of human serum are chemically closely akin to those of colostrum. By the addition of serum, even in small quantities, to the feeding a great increase in weight is obtained, which continues as long as serum

is given. One cubic centimeter per kilogram of body weight of a mixture composed of 25 Gm. of serum, 25 Gm. of dextrose and 50 Gm. of water was given. Human serum leads to a greater increase in weight than horse serum, and the latter brings about a greater increase than the same amount of pure casein. No digestive disturbances, allergic reactions or other injurious effects were observed. Of 4 infants who were given horse serum for more than two weeks, neither antigens (horse antigen) nor antibodies against them could be demonstrated in the blood.

WALLGREN, Stockholm, Sweden.

Acute Contagious Diseases

ACUTE ANTERIOR POLIOMYELITIS (HEINE-MEDIN DISEASE) DURING MENINGOCOCCIC MENINGITIS PRECEDED BY PHYSICAL TRAUMA: REPORT OF TWO CASES. ANSELMO CALAMARI, Riv. di clin. pediat. **44**:411 (July) 1946.

Two cases of acute anterior poliomyelitis (Heine-Medin disease), in which physical trauma occurred a few days before, with the onset of the initial symptoms during meningococcic meningitis, are described by the author. The exceptional association of the meningococcus and the poliomyelitis virus is emphasized. This association is fully discussed clinically in both cases, as proved by laboratory examinations, and by anatomicohistologic observations, which were made in 1 case. The author expresses the belief that, apart from the physical trauma preceding the disease, the meningococcic infection can be considered as an "infectious trauma" with respect to the poliomyelitis, which followed in a violent and rapidly fatal form.

FROM THE AUTHOR'S SUMMARY.

PREDISPOSITION TO ACUTE ANTERIOR POLIOMYELITIS. OLE CHRISTENSEN, Nord. med. (Hospitalstid.) **28**:2573 (Dec. 14) 1945.

Family researches suggest the existence of a hereditary predisposition to infantile paralysis. This predisposition appears to be connected with a general predisposition to other neuropsychiatric disorders. Several authors pointed out the significance of a special constitutional type, with certain endocrine features. Pregnancy is a predisposing factor. Tonsillectomy, adenotomy and severe trauma may provoke the disease. Enteritis and other infections are also stated to be causative factors, as well as excessive physical exertion with improper cooling. The question whether a deficiency of vitamin E may play a part as a predisposing factor is discussed.

WALLGREN, Stockholm, Sweden.

POLIOMYELITIS IN MOTHERS AND THEIR NEWBORN INFANTS. KULE PALMSTIERNA, Nord. med. (Hygiea) **27**:1778 (Sept. 7) 1945.

The author reports 2 cases of poliomyelitis in pregnant women (tetrtiparas), 32 and 42 years of age, respectively. In the first case, the woman in her ninth month of pregnancy manifested paresis of the respiratory muscles. She died two days later. Shortly before her death she was delivered by cesarean section. The infant weighed 2,630 Gm. and was in good condition at birth. On the twelfth day of life he displayed signs and symptoms of poliomyelitis with severe paralysis of the legs and typical changes in the spinal fluid. At the age of 4 months paresis was still evident.

In the second case, the woman had a normal delivery and signs of poliomyelitis were apparent on the seventh day post partum. Five days after the beginning of the mother's illness, the infant showed signs of abortive poliomyelitis, with typical

changes in the spinal fluid, but no paresis. The infant was in good health at the age of 4 months.

WALLGREN, Stockholm, Sweden.

DIPHTHERIA DURING THE FIRST YEAR OF LIFE. J. BOE, Nord. med. (Med. rev., Bergen) **28**:2030 (Oct. 5) 1945.

The author reports his observations on 106 cases of diphtheria in infants, 15 (14 per cent) of whom died. The disease in infants is often misdiagnosed, as the clinical signs may differ considerably from those in older children. Attention is called especially to nasal diphtheria in infants; a persistent rhinitis, often unilateral, may be the only symptom. The morbid condition often is not recognized until the nutritional state of the child is poor and secondary infections have occurred. Of the 106 infants, 14 had croup, 5 of whom died. The effect of serum therapy was not evident. Vaccination during the first year of life is not usually successful. As a prophylactic measure in times of epidemic, the author recommends that the mother be vaccinated several months before delivery if she reacts positively to the Schick test.

WALLGREN, Stockholm, Sweden.

DETERMINATION OF IMMUNITY TO DIPHTHERIA IN MOTHERS AND THEIR INFANTS. B. VAHLQUIST and N. G. PERSSON, Svenska läk.-tidning. **42**:3037 (Dec. 7) 1945.

Antitoxin titrations of the blood serum were performed for 56 mothers and their infants, of whom 35 were newborn, 14, 2 to 3 months of age and 15, 6 to 8 months of age. Only 10 per cent of the mothers had an antitoxin titer that could confer immunity; blood from the other 90 per cent showed little or no antitoxin. The deficient immunity of the mothers is considered to be the reason that at present only a few infants are immune to diphtheria during their first months of life. There is risk of an increased frequency of the disease in infants owing to this lack of protection. The authors maintain that the deficient immunity to diphtheria in the mothers is due to the extremely low morbidity rate of the disease in Sweden.

WALLGREN, Stockholm, Sweden.

Acute Infectious Diseases

INFANTILE VISCERAL LEISHMANIASIS IN FIESOLE, ITALY: REPORT OF A CASE. A. GALEOTTI FLORI, Riv. di clin. pediat. **40**:359 (June) 1942.

A clinical report, with observations at autopsy, is given of the first case of leishmaniasis to be detected in Tuscany or in the province of Florence. It is suspected that the source of the infection was an itinerant Sicilian family and that it was carried through an intermediate host, such as a mosquito or a flea.

HIGGINS, Boston.

COMPRESSION OF VERTEBRAE CAUSED BY TETANUS. AAGE RANDLOW-MADSEN, Nord. med. (Hospitalstid.) **26**:1299 (June 29) 1945.

A case of kyphosis following compression of the vertebrae caused by tetanus in a boy 11 years of age is presented. The morbid picture resembled injuries to the spine caused by other types of convulsions, especially those produced from treatment of mental disorders with artificial shock.

WALLGREN, Stockholm, Sweden.

NEPHROCALCINOSIS ASSOCIATED WITH HYPERCHLORAEMIA. W. W. PAYNE, Proc. Roy. Soc. Med. **39**:133 (Jan.) 1946.

A girl 10½ years of age had "kidney trouble" from the age of 1½ years. Examination revealed a small, thin, intelligent child with knock knee. Urine showed 50 mg. of albumin per hundred cubic centimeters, with no casts or crystals; Addis count showed 8,000,000 red blood cells and 220,000,000 white blood cells. A roentgenogram showed multiple deposits of calcium density in both kidneys. The bones showed thinning of the cortex. Results of complete blood studies before and after treatment are given in the report. Treatment consisted in the administration of 60 cc. of the following solution daily: citric acid, 140 Gm., sodium citrate, 98 Gm., with water to make 1,000 cc. She was also given 30,000 U.S.P. units daily of vitamin D.

WILLIAMSON, New Orleans.

PATHOGENESIS OF THE HYPERPYRETIC TYPE OF THE MALIGN SYNDROME IN CHILDREN. YNGVE AKERRÉN, Nord. med. (Hygiea) **25**:608 (March 23) 1945.

The hyperpyretic syndrome is characterized by an extreme elevation in temperature, disturbance in the consciousness, convulsions, weak pulse and extreme paleness, and often by coldness of the extremities. These signs are typical for shock, which the author states is also produced by the hyperpyrexia; successful treatment of the condition eliminates the occurrence of the malign syndrome in these cases. In the fatal cases death is often due to the extreme elevation in temperature. The hyperpyrexia depends on two factors, the infection and the lack of control of physical thermoregulation. The author emphasizes the importance of close supervision of the temperature and of the establishment of prophylactic measures against hyperpyrexia in febrile diseases in infants and small children.

WALLGREN, Stockholm, Sweden.

Chronic Infectious Diseases

ALLERGIC NATURE OF CLINICAL FORMS OF TUBERCULOUS MENINGITIS. L. AURICCHIO, Pediatria **54**:353, 1946.

The author reports the development, in 2 children with specific pulmonary infiltration, of clinical forms of meningitis which seemed to be of tuberculous origin, but which unexpectedly was cured. After presenting the hypothesis concerning the origin of these forms of "serous meningitis in subjects with tuberculosis," the author states his belief that the observed meningeal syndromes are closely related to tuberculosis. He states that the rapid regress of meningeal inflammation in such cases cannot be easily explained unless it is considered as a specific allergic manifestation.

FROM THE AUTHOR'S SUMMARY.

AN EPIDEMIC OF ERYTHEMA NODOSUM AND MEASLES IN AN INSTITUTION. R. GIUNTINI, Riv. di clin. pediat. **41**:129 (March) 1943.

In an institution caring for 31 children 2½ to 15 years of age, active tuberculosis developed in 1 child. One month later, a febrile illness which proved to be erythema nodosum developed in 3 other children; each of the 3 had a strongly positive reaction to tuberculin. Shortly afterward an epidemic of measles developed which involved 7 children; convalescent serum may have prevented its spread. In 1 of these children active pulmonary tuberculosis developed; 3 others had a prolonged convalescence.

Of the total of 31 children, clinical manifestations of tuberculosis developed in 7; 10 others showed a strongly positive reaction to tuberculin and roentgenographic signs of the disease; 3 had latent tuberculosis, but with a negative reaction to the tuberculin test because of the measles, and 11 showed no clinical or roentgenologic manifestations of the disease. The frequent association of erythema nodosum with tuberculosis is discussed, as well as the danger of measles to a tuberculous child.

Of 23 cases of erythema nodosum seen in the pediatric clinic at Florence, Italy, over twenty years, 12 were of boys and 11 of girls whose ages ranged from 3 to 10 years; 60 per cent of the children came from families known to have tuberculous infections; all the children had positive reactions to tuberculin, and 15 of them showed roentgenographic evidence of tuberculosis.

HIGGINS, Boston.

GIGANTIC TUBERCULOUS CAVITY: REPORT OF A CASE IN AN INFANT. PASQUALE DE CAPRIO, Pediatria **54**:445, 1946.

The author reports a case of giant tuberculous cavity in an infant 8 months of age. After discussing the clinical and roentgenologic observations post mortem which could lead to the erroneous interpretation of the cavity as a hydropneumothorax or a piopneumothorax, he describes the case, according to Monaldi's views, as the clinicobiologic cycle of pulmonary tuberculosis in first infections, pointing out the characteristic rhythm of the lesion which in the nursing infant can be manifold, discontinuous and superimposed as an expression of its various phases.

FROM THE AUTHOR'S SUMMARY.

NEGATIVE REACTIONS TO TUBERCULIN IN TUBERCULOUS INFECTIONS. M. REALE, Riv. di clin. pediat. **41**:163 (March) 1943.

The author discusses the incidence of negative reactions to tuberculin in patients with active or healed tuberculosis, making use of personally obtained data and of reports in the literature.

HIGGINS, Boston.

TUBERCULOSIS AND SCARLET FEVER. ERIK HENRIKSEN, Nord. med. (Hospitalstid.) **26**:1087 (May 25) 1945.

The author reports on 53 children, 1 to 14 years of age, with tuberculosis who contracted scarlet fever. In only 1 child was there an aggravation of the tuberculosis. Three months after the scarlet fever subsided, 2 of the children died from tuberculous meningitis, and pleurisy developed in 2 other children. The incidence of meningitis and pleurisy is no higher statistically in this group than in a control group of tuberculous children who did not have scarlet fever.

WALLGREN, Stockholm, Sweden.

CONGENITAL SYPHILIS IN THE SECOND GENERATION. BERNHARD LANDTMAN, Nord. med. (Finska läk-sällsk. handl.) **27**:1705 (Aug. 31) 1945.

A full term female infant 2½ months of age had had an exanthem on the palms of the hands and the soles of the feet since her third week of life. Shortly before her admission to the hospital rhinitis and fever began. The Wassermann reaction to the blood was positive. The infant died of gastroenteritis two weeks after admission. Postmortem examination revealed osteitic defects of the skull. The parents were not aware of any syphilitic infection. While the Wassermann

reaction of the blood of both parents was negative, the mother had a positive reaction to the Kahn test. When she was 2 months old, syphilis had been demonstrated in her and her mother, both of whom showed positive reactions to the Wassermann test. She had been treated with inunction of a mercurial compound. When she grew older, she was unaware of the previous syphilitic infection.

WALLGREN, Stockholm, Sweden.

VACCINATION WITH SCARIFICATION METHOD. VAGN SINDBJERG-HANSEN and POUL MÖLLER, Nord. med. (Hospitalstid.) **28**:2018 (Oct. 5) 1945.

Twenty-two newborn infants were vaccinated with bacillus Calmette-Guérin by scarification. A vaccine containing 20 mg. of BCG per cubic centimeter was used. The scarified area of the cutis was covered with a patch for the first twenty-four hours after vaccination. Only an insignificant local reaction of short duration occurred. Eighty-six per cent of the infants became sensitive to tuberculin, which corresponds fairly well to the result of intradermal vaccination. Allergy occurs somewhat more rapidly with the latter method. Since vaccination by the intradermal method, if improperly performed, may cause local abscesses, the scarification method, which is simpler, is recommended for those who only occasionally perform vaccinations.

WALLGREN, Stockholm, Sweden.

TUBERCULOUS PERICARDITIS. ARVID WALLGREN, Nord. med. (Hygiea) **25**:32 (Jan. 5) 1945.

A boy 6½ years of age who had had ulcerous colitis since 1941 became ill in December 1943 with erythema nodosum and right-sided primary pulmonary tuberculosis. About one month later, pericarditis developed, with signs of cardiac failure and enlargement of the liver. No signs or symptoms of rheumatic fever were present. During a fortnight the child's condition was poor, then it began to improve. The cardiac changes disappeared; the temperature became normal, and the boy was eventually discharged from the hospital with only slight enlargement of the heart and a normal electrocardiogram.

WALLGREN, Stockholm, Sweden.

Diseases of Blood, Heart and Blood Vessels and Spleen

FAMILIAL ERYTHROBLASTIC (COOLEY'S) ANEMIA: REPORT OF A CASE. A. INGIULLA, Riv. di clin. pediat. **41**:65 (Feb.) 1943.

A report of a case of familial erythroblastic (Cooley's) anemia in a girl between 3 and 7 months of age is given. The rare occurrence of the disease in the city of Florence, Italy, and in Tuscany is mentioned.

HIGGINS, Boston.

VARIATIONS IN CHEMICAL COMPOSITION OF BLOOD AND OF SERUM FROM CUTANEOUS VESICLES AFTER DRINKING WATER: OBSERVATIONS ON NORMAL CHILDREN AND ON CHILDREN WITH ENDOCRINE DYSCRASIAS. T. CAPECCHI, Riv. di clin. pediat. **41**:417 (Aug.) 1943.

Observations are reported on 6 children with mongolism, 4 with mild myxedema and 6 normal controls, including 2 adults. The effect of drinking 16 cc. water per kilogram of body weight on the chemistry of the blood (hemoglobin concentration and water, chloride and nonprotein nitrogen levels) was studied over a period of four hours. There was a parallel diminution of the hemoglobin and chloride of the blood over the first two hours after drinking the water; this diminu-

tion was greater in normal children than in adults, slightly greater in the normal children than in those with mongolism and much greater in the normal children than in those with myxedema. Serum was obtained for analysis from vesicles caused by a preparation of Cantharis; the water content of this serum was higher in the children with myxedema than in the normal children.

HIGGINS, Boston.

PROTHROMBIN TIME IN NORMAL SARDINIAN CHILDREN. P. PINNA, Riv. di clin. pediat. **44**:463 (Aug.) 1946.

The author observed a peculiar frequency of hemorrhage in children with the infective and toxic syndromes in this region. He therefore made determinations of the prothrombin time in those children who could be considered normal physiologically.

He discovered that in 95 of 100 children examined the prothrombin time was more or less prolonged, with enough constancy in individual differences to enable him to admit the possibility of a constitutional alteration probably associated with factors acting through many generations in Sardinia.

FROM THE AUTHOR'S SUMMARY.

DYSPNEA PRODUCED BY RIGHT-SIDED AORTIC ARCH. NIELS FIIL and ERLING HALD, Nord. med. (Hospitalstid.) **27**:1448 (July 20) 1945.

A case of congenital malformation of the heart in a female infant 14 days of age is reported. She had been dyspneic since birth, and deterioration of the condition with cyanosis and stridor occurred occasionally. Roentgenographically, stenosis of the trachea at the bifurcation was demonstrated. Heart disease was not suspected, as clinical signs were normal. The tentative diagnosis of tumor was made, and tracheoscopy was performed, with biopsy of an excised portion of the treacheal mucosa. The infant died shortly afterward. Postmortem examination revealed a persistent fourth embryonic arterial arch and the absence of the proximal part of the left fourth arch. Thus, a semicircle was formed which enclosed the trachea and the esophagus from the right side and caused pressure on these organs. The result was stenosis of the trachea. The stenosis of the esophagus produced no symptoms.

WALLGREN, Stockholm, Sweden.

PREEXCITATION IN CHILDHOOD. JÖRCEN JÖRGENSEN, NORD. med. (Hospitalistid.) **27**:1655 (Aug. 24) 1945.

A case of preexcitation of the type of Clerc, Levy and Cristesco (*Arch. d. mal. du coeur* **31**:569, 1938) in a male infant 6 months of age with paroxysmal tachycardia is reported. Attention is directed to the probable importance of this electrocardiographic abnormality in the diagnosis of paroxysmal tachycardia in children. The author expresses the belief that the syndrome of Wolff, Parkinson and White (*Am. Heart J.* **5**:685, 1930) is relatively frequent in children, although only 6 cases have been reported.

WALLGREN, Stockholm, Sweden.

HYPOPLASTIC ANEMIA. WILHELM BERGMAN, Nord. med. (Hygiea) **25**:35 (Jan. 5) 1945.

A case of hypoplastic anemia in a girl 1½ years of age, who had had a blood disorder since she was 3 months old, is reported. Her weight at birth was normal, and she received mixed feeding. At 2 months of age she was first seen. At that time

she had a hemoglobin content of 81 per cent, which three weeks later had decreased to 67 per cent. From her third month on, the hemoglobin varied between 75 and 25 per cent, and on one occasion it was only 14 per cent. The number of red blood cells varied from 3,000,000 to 730,000. There were no signs of regeneration of the peripheral blood cells, and the bone marrow showed an elective lesion of erythropoiesis, with hyperplasia of the reticulum. The white blood cells were normal. The spleen was not palpable. The serum iron value was increased to 0.4 mg. per hundred cubic centimeters. Acid values in the stomach remained normal. The Wassermann reaction was negative. The child was physically and psychically underdeveloped. Treatment with iron, liver, arsenic and vitamin B was without effect. Blood transfusions had to be made every second month. The manner in which the girl tolerated the low blood values was surprising. The cause of the condition is unknown.

WALLGREN, Stockholm, Sweden.

PITUITARY BASOPHILISM (CUSHING). IVAR NILSBY, Nord. med. (Hygiea) **28**:2379 (Nov. 9) 1945.

For one year before her admission to the hospital, a girl 15 years of age was subject to rapidly increasing adiposity, headaches, fatigue, cessation of menses and, toward the last, such severe backaches that she had to remain in bed. On examination she presented the typical picture of Cushing's syndrome: adiposity of face, neck and trunk, dry skin with glowing face, pronounced striae atrophicae, hypertonia, erythemia and osteoporosis. There were no signs of virilism. Potassium and calcium levels in the serum were decreased, while the phosphorus level was increased. Roentgenographic examination disclosed that the right adrenal gland was the site of a tumor, which was surgically removed. This histologic diagnosis was adenocarcinoma. Several days later the girl died, and autopsy revealed that the tumor had infiltrated the adjacent tissues and had metastasized in the lungs. The hypophysis showed diffuse hyaline change in the basophilic cells. The other endocrine glands were normal. Special stress is given the fact that the absence of virilism does not rule out the presence of a malignant tumor of the adrenal gland.

WALLGREN, Stockholm, Sweden.

AGRANULOCYTOSIS AFTER TREATMENT WITH SALICYL-AZO-SULFAPYRIDINE ("SALAZOPYRINE"). ARNE NJA, Nord. med. (Norsk mag. f. laegevidensk.) **28**:2334 (Nov. 2) 1945.

The author reports a case of agranulocytosis in a boy 9 years of age caused by salicyl-azo-sulfapyridine ("salazopyrine"). No granulocytes were seen. The boy had multiple rheumatoid arthritis (Still's disease), and it was the second time within one year that he displayed agranulocytosis produced by this drug. He recovered after twelve days of treatment with thymine.

WALLGREN, Stockholm, Sweden.

Diseases of Nose, Throat and Ear

THE MIDDLE EAR AS SITE OF INOCULATION IN TUBERCULOSIS. C. M. KIZOULIS, Arch. franç. de pédiat. **3**:156, 1946.

The presence of an extrapulmonary seat of inoculation in tuberculosis has always aroused great scientific and clinical interest. Among these centers, the middle ear is the most infrequent. A fully documented case of inoculation of the middle ear is reported. The patient, a baby 1 month of age, was seen to have retromaxillary adenitis. There was moderate anemia, with red blood cells numbering 3,000,000

and white cells 6,200, with 75 per cent lymphocytes. At the age of 2½ months the adenitis had progressed; there was fever, and a purulent secretion was detected in the right ear. Five days later this otorrhea was complicated with paralysis of the right facial nerve. At this time, the Pirquet reaction was negative, but there were suggestive constitutional symptoms, such as pallor, loss of appetite and failure to gain weight. When the patient was 3 months of age, the reaction to the Mantoux test was positive. The reaction to the Bordet-Wassermann test had been negative from birth. Examinations of the contents of the stomach and roentgenographic investigations revealed nothing abnormal; the adenitis advanced; the aural discharge continued, and, in spite of treatment with sulfonamide compounds, the tympanic membrane showed gradual destruction. Because tuberculosis in its early stages was suspected, one of the larger tumefactions was punctured, and the aspirated fluid was inoculated into a guinea pig. Soon after Myocobacterium tuberculosis was seen in the purulent discharge from the ear. The guinea pig showed the classic dissemination of tuberculosis several weeks after inoculation. The infant died from pneumococcic meningitis at the age of 23 months. Autopsy revealed the characteristic lesions of tuberculosis in the right ear and the retromaxillary glands.

AMESSE, Denver.

ACIDOSIS IN ACUTE SUPPURATIVE OTITIS MEDIA IN INFANTS. ESBEN KIRK, Nord. med. (Hospitalstid.) **25**:309 (Feb. 16) 1945; **28**:2235 (Oct. 26) 1945.

Acidosis is frequently encountered in severe cases of acute suppurative otitis media in infants. It is due chiefly to the accumulation of organic acids, which are supposed to be produced mainly through the action of toxic bacterial products on the intermediary metabolic factors. The acidosis is often accompanied with pronounced hyperpnea. This hyperpnea may lead to diagnostic errors, as it may be attributed to pneumonia. In cases of severe acidosis and dyspnea, parenteral injections of isotonic sodium bicarbonate solution will often relieve the dyspnea and improve the general condition.

Aciosis was demonstrated in 20 feeble infants with suppurative otitis media, in half of whom the condition was severe. The treatment consisted of subcutaneous or intrasternal injection of isotonic (1.3 per cent) sodium bicarbonate solution.

WALLGREN, Stockholm, Sweden.

BACTERIOLOGIC STUDIES OF OTITIS MEDIA IN INFANTS. J. C. NIELSEN, Nord. med. (Hospitalstid.) **28**:2236 (Oct. 26) 1945.

Otitis media during the first year of life is caused mostly by pneumococci, chiefly types 19, 14, 9, 23 and 18, as well as type 3 which is found relatively often. A large proportion of cases is due to the bacillus of Pfeiffer, whereas the hemolytic streptococci are subordinate causative agents.

WALLGREN, Stockholm, Sweden.

OTITIS MEDIA IN CHILDREN AT THE KOMMUNEHOSPITAL OF COPENHAGEN. H. A. ANDERSEN, Nord. med. (Hospitalstid.) **28**:2232 (Oct. 26) 1945.

During the last twenty-one years 1,300 children under 2 years of age with otitis media were treated at the Kommunehospital, Copenhagen, Denmark. The incidence for operation was reduced to 25 per cent from the former frequency of 50 to 60 per cent. At the same time, the average stay at the hospital increased from about three weeks to six to eight weeks, an expression of the more conservative treatment. The time of operation in the course of the disease has changed too, the operation as a rule not being performed till about fifty days have elapsed. During the same span of years the mortality has also been reduced. It is doubtful,

however, that the more favorable prognosis may be attributed to the conservative treatment. It is due rather to chemotherapy, for during recent years complications involving the lungs and hyperpyrexias have caused no deaths. The influence of chemotherapy on the course of the otitis has, however, not been evident. The author emphasizes the importance of paracentesis in case of retention of pus. He warns against adenotomy in the presence of otitis. He states that poor social circumstances have a bad influence on the prognosis of the otitis and that many of the children from the poorer social classes are above all in need of proper care and feeding.

WALLGREN, Stockholm, Sweden.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

PERITONITIS CAUSED BY CHOLECYSTITIS COMPLICATING TYPHOID IN CHILDREN: REPORT OF TWO CASES. F. BAZAN and E. SUJOY, Arch. argent. de pediat. **26**:3 (July) 1946.

1. Cholecystitis complicating typhoid in childhood is extremely severe when suppuration and necrosis of the wall of the gallbladder is produced.

2. Surgical treatment, even early, does not always save the patient's life, as some statistics (Prier's) suggest.

3. Necrosis of the wall of the gallbladder is sometimes an incidental observation at autopsy, the symptoms of the necrosis being obscured by the complex symptoms of the severe typhoid.

FROM THE AUTHORS' CONCLUSIONS.

UMBILICAL HERNIA IN CHILDREN. OVE RIISFELDT, Nord. med. **28**:2367 (Nov. 9) 1945.

The incidence of umbilical hernia in Danish children is 25 per cent in newborn infants, 25 per cent at 3 months, 11.5 per cent at 1 year, 4 per cent at 7 years and 0.25 per cent at 14 years of age. Spontaneous healing takes place in 56 per cent of these children before the end of the first year and in 70 to 90 per cent before the fourteenth year. Seventy to 90 per cent of the hernias present at the age of 7 years disappear without treatment.

WALLGREN, Stockholm, Sweden.

SIALOLITHIASIS WITH SPONTANEOUS DISCHARGE OF THE CONCREMENT IN A GIRL FOURTEEN YEARS OF AGE. TROELS VARMING, Nord. med. (Hospitalstid.) **28**:2447 (Nov. 23) 1945.

A 14 year old girl had difficulties in deglutition and speech. Signs of swelling appeared beneath the tongue and on the left side of the neck, attended with a rise in temperature. Some days later a concrement of oblong shape, about 2.5 cm. long, was spontaneously discharged from the left submaxillary duct.

WALLGREN, Stockholm, Sweden.

EPIDEMIC HEPATITIS IN INFANTS. KARIN EEK, Nord. med. (Hygiea) **25**:37 (Jan. 5) 1945.

Five cases of hepatitis in infants 4 weeks to 3 months of age are reported. The course of the disease corresponded to that of epidemic hepatitis, and in 4 cases the source of infection was detected (the incubation period was three and a half to six weeks); in the fifth case the nurse became ill twenty-four days after contact with the child. Four of the children were discharged from the hospital in good condition after three weeks to three months of treatment; the fifth child died, and

the postmortem examination showed pronounced proliferation of connective tissue and cellular infiltration of the liver. The cause of death was cerebral hemorrhage.

WALLGREN, Stockholm, Sweden.

MEGACOLON IN NEWBORN INFANTS. T. EHRENPREIS, Nord. med. (Hygiea) **27**:1419 (July 13) 1945.

The author studied the initial signs and symptoms and the development of negacolon in 9 newborn infants. The primary factor is a disturbance of the mechanism of evacuation in the colon. Examinations during the first ten days of life already revealed unsatisfactory evacuation. The anatomic picture of megacolon developed secondarily in three weeks to three and a half months in 4 of the cases, but that interval may be shorter or longer in other cases. Thus, megacolon may be characterized as a dilatation and hypertrophy of the colon caused by a functional disturbance of the normal mechanism of evacuation.

WALLGREN, Stockholm, Sweden.

CELIAC DISEASE IN UNIOVULAR TWINS. SVEN HOLMGREN, Nord. med. (Hygiea) **28**:2252 (Oct. 26) 1945.

At the age of 2½ years, twin girls had celiac disease at the same time, after having whooping cough. The disease developed in the characteristic manner. The article is well illustrated.

WALLGREN, Stockholm, Sweden.

INTESTINAL ATRESIA. JOHANNES LEWIS-JONSSON, Nord. med. (Hygiea) **28**:2558 (Dec. 7) 1945.

Atresia of the small intestine in a newborn infant was successfully treated surgically on the third day of life. Enteroanastomosis was performed, and the infant was discharged from the hospital in good condition.

WALLGREN, Stockholm, Sweden.

Nervous Diseases

TREATMENT OF AN UNUSUAL SUBDURAL HYDROMA (EXTERNAL HYDROCEPHALUS). WALTER E. DANDY, Arch. Surg. **52**:421 (April) 1946.

Two types of external hydrocephalus are described: the congenital and posttraumatic. In the former type the arachnoid membrane is torn beyond the cistern; then fluid pours into the subdural space. The case reported was of the traumatic type. In spite of repeated taps and drainage, the accumulation of fluid continued into the subdural space. Several operations were performed before the subdural hydroma healed. In the final operation no definite fistula was disclosed; so it was necessary to iodinize the entire area along the falx to insure its inclusion. Complete recovery followed. The relation of subdural hydroma to absorption of cerebrospinal fluid is discussed.

KAISER, Rochester, N. Y.

TUBEROUS SCLEROSIS (BOURNEVILLE-PRINGLE DISEASE). D. HOJER-PEDERSEN, Nord. med. (Hospitalstid.) **26**:763 (April 6) 1945.

A boy of 13 years of age who had always showed a mental deficiency and who for the last seven years had had adenoma sebaceum, especially on the face, displayed rapidly developing signs of intracranial hypertension. He was an imbecile

and had incipient edema of the primarily atrophied papillas and greatly impaired vision. He was of infantile hypoplastic proportions and showed pronounced cutaneous, mucous and retinal changes typical of tuberous sclerosis. Ventriculography disclosed a tumor in the right lateral ventricle. This tumor was removed; its histologic classification was magnocellular glioblastoma. Examination of the family showed a dominant hereditary trait. Reexamination six months after operation revealed no change in vision, but the child's condition was otherwise satisfactory.

WALLGREN, Stockholm, Sweden.

SEROUS MENINGITIS IN EARLY INFANCY. H. MOSSBERG, Nord. med. (Hygiea) **25**:29 (Jan. 5) 1945.

The author reports 6 cases of acute serous meningitis in infants 2 weeks to 3 months of age who were admitted to the hospital from September to November 1943. All the children had convulsions, which were the immediate reason for admission; some of the children had, in addition, vomiting and fever. Clinical signs of meningitis were scanty. Spinal fluid showed somewhat increased globulin content, while the number of cells varied from 8 to 122 per cubic millimeter, most of them monouclear forms. The Wassermann reaction was negative. Culture of the fluid yielded no pathogens. The reaction to the tuberculin test (Mantoux, 1 mg.) was negative. The course of the illness was benign, and all the infants were discharged in good health. The outbreak had no relation to poliomyelitis or any other known infection. This disease is supposed to be identical with the acute aseptic meningitis described by Wallgren in 1925.

WALLGREN, Stockholm, Sweden.

Diseases of the Genitourinary Tract

FREQUENCY OF INTESTINAL PARASITOSIS IN CHILDREN. RENATO FEROLA, Pediatria **54**:-426, 1946.

The author gives the results of examination for parasites in 244 specimens of children's feces. (These examinations were made in collaboration with the Italian Medical Nutrition Mission, United Nations Relief and Rehabilitation Administration.) He noticed that intestinal parasites are often present which do not impair the general nutritive state. Among the worms most frequently seen were the Oxyuris, Ascaris and Trichuris, and among the protozoa were the Giardia, Endamoeba coli and Endamoeba histolytica.

FROM THE AUTHOR'S SUMMARY.

TYPHOID HEPATITIS: REPORT OF A CASE. ARRIGO DE LUCA, Pediatria **54**:457, 1946.

After a rapid review of the literature on the incidence of hepatitis during typhoid fever, the author describes the development of a case which attracted his attention by its clinical features. Results of various researches led the author to the belief that the relation of the hepatic involvement and the typhoid infection can be explained as the expression of a process caused by the action of the reticuloendothetial system, affecting particularly the mesenchymal section of the liver.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF RENAL ADENOSARCOMA (WILMS'S TUMOR). STIG BERGLUND, Nord. med. (Hygiea) **25**:276 (Feb. 9) 1945.

The author reports on 13 patients with Wilms's renal adenosarcoma treated at the radiotherapeutic clinic in Stockholm, Sweden. Of the 13 children, 6 were boys. The 2 infants in the series were 9 and 21 months of age; 4 children were 4 years

of age; 3 were 5 years old; 1 was 6, 2 were 7 and 1 was 16 years of age. Eleven of the children had received incomplete surgical treatment because of the size of the tumor; in 1 child the growth was small enough to be completely removed, and this child was still living, free from symptoms, eighteen months later. Only 1 child received primarily roentgenologic treatment with good effect on the tumor; it was decreased to one-tenth the original size. In this child, however, the growth soon metastasized to the lungs. In this series the time from the diagnosis of the illness to the death of the child varied from one to sixteen months. The author's experience shows that Wilms's tumor often is radiosensitive, and he recommends early roentgenologic and surgical treatment as the only procedure giving good results.

WALLGREN, Stockholm, Sweden.

Diseases of the Ductless Gland; Endocrinology

THE GENERAL ADAPTATION SYNDROME AND THE DISEASE OF ADAPTATION. HANS SELYE, J. Allergy **17**:231 (July) 1946.

A review of the literature pertaining to the general adaptation syndrome is given because of investigations which suggest that some diseases (hypertension, nephrosclerosis and the rheumatic diseases) may represent by-products of the endocrine reactions which are at play in the general adaptation syndrome.

An extensive bibliography is included.

HOYER, Cincinnati.

URINARY SECRETION OF ACETONE BODIES IN DIABETIC KETOSIS. A. P. BRIGGS, Proc. Soc. Exper. Biol. & Med. **63**:15 (Oct.) 1946.

The quantitative determination of the total acetone bodies and acetone in the blood and urine was made in 12 patients with diabetic ketosis, 5 of whom were in coma. The concentrations of acetone in the blood and urine were strikingly similar. This finding tends to support the previously presented idea that acetone is excreted into the urine by the physical processes of filtration and diffusion. In 2 of the patients in coma evidence of renal block was shown by finding the total acetone body content of the urine to be less than that of the blood. These studies appear to demonstrate that a functional disturbance of the renal tubules, with elevations of the threshold for diacetic acid, accounts for the occasional presence of a negative reaction for diacetic acid in the urine of the patients in diabetic coma. However, it is not clear to why such a phenomenon occasionally occurs.

HANSEN, Galveston, Texas.

OPOTHERAPY IN INFANCY. PERINA WINOCUR, Arch. argent. de pediat. **25**:276 (April) 1946.

A brief summary of the role, pharmacologic aspects and therapeutic uses of the commonest hormones is presented.

The author draws the following conclusions:

The pediatrician must handle powdered thyroid carefully. This powder alone is sufficient for treatment of myxedema and the various degrees of hypothyroidism. Parenteral use of this hormone is not necessary. The chorionic gonadatropin is used for ectopia of the testis. The other gonodatropins are of little use in infancy.

The parathyroid hormone should be used only in urgent cases (idiopathic or postoperative absence of the parathyroid gland). Afterward it is advisable to continue with dihydrotachysterol, viosterol, calcium salts and proper dietary acids.

The growth hormone may be useful in well determined cases of delay in growth.

For acute adrenal insufficiency and adrenal cortical hypofunction (Addison's disease), the extract of the total adrenal cortex and desoxycorticosterone may be used; however, both require important supplementary treatment.

For the treatment of diabetes, in addition to the use of insulin, increase in the alterations produced by the hormone deficit must be avoided by administration of an adequate diet and saline or glucose solutions.

ROJAS, Boston.

ACTION OF ETHER AND ALCOHOL-BENZENE EXTRACTS FROM THE THYMUS IN CHILDREN WITH NORMAL AND PATHOLOGIC METABOLISM OF GLYCOGEN. ANGELO CHIEFFI and LELIO NASSI, Riv. di clin. pediat. **43**:50, 1945.

The authors, in continuing their researches, studied the effects of lipid extracts from the thymus (ether and alcohol-benzene extracts) on glycemia in subjects with normal and with pathologic sugar metabolism.

In normal persons, an almost constant increase in the blood sugar level was evident, especially with thymus extracts obtained by the special technic (alcohol-benzene extraction). The persistence of the biologic effect, even in the acetone fraction obtained by saponification of these extracts, induced the authors to express the opinion that the active part of the extract must be a sterol (thymus-sterol). The increase in blood sugar levels brought about by thymus extracts is also evident in the curves for epinephrine and for insulin.

These extracts had no effect on persons with diabetes mellitus, while in a patient with glycogenosis (von Gierke's disease) the authors observed such a pronounced modification of the blood sugar levels as to consider the extracts of almost therapeutic value in this disease and to suggest their further use.

FROM THE AUTHOR'S SUMMARY.

INFLUENCE OF HORMONES ON THE CREATINE-CREATININE METABOLISM OF CHILDREN. A. GENTILI, Riv. di clin. pediat. **40**:480 (Aug.) 1942.

The urinary excretion of creatine and creatinine was determined in observations lasting twenty-three to thirty-seven days on 6 children, 3 girls and 3 boys, 6 to 9 years of age. When either testosterone propionate U.S.P. (10 mg. daily) or estradiol benzoate U.S.P. (1 mg. daily) was given by hypodermic injection to a child for four days, the creatine excretion in the urine ceased within three days. Creatine again appeared in the urine after the drug was discontinued. The boys and girls reacted similary to each of the two hormones. Gentili expresses the opinion that this action was direct and that it was not caused by the pharmacologic effect on the thyroid or pituitary glands of the children.

HIGGINS, Boston.

HYPERFUNCTION OF THE ADRENAL CORTEX IN CHILDREN BEFORE PUBERTY. ROLF LUFT, Nord. med. (Hygiea) **27**:1773 (Sept. 7) 1945.

The author describes 4 children with genital abnormalities and an increased excretion of urinary andrin and 17-ketosteroids. The first child was a boy 7 years of age with carcinoma of the adrenal cortex, abnormal growth of the penis and beginning growth of pubic hair. The second child was a boy, aged 2½ years, who showed precocious body development, hypertrophy of the penis and growth of pubic hair. Exploratory laparotomy disclosed hyperplasia of the cortex of the left adrenal gland. A girl 7 years of age had hermaphroditismus ovarialis (seen on laparotomy). In the last child, a girl 4 years of age, decided hypertrophy of the clitoris was the only genital abnormality. The increased excretion of 17-ketosteroids and of biologically active androgens in the urine is regarded as a sign of increased function of the adrental cortex. The article is illustrated with photographs.

WALLGREN, Stockholm, Sweden.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Bornehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana, Cuba.

International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quai Wilson, Geneva, Switzerland.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Asociacion de Pediatras de Cataluna

President: Dr. Emilio Roviralta, Policlinico, Platon 1, Barcelona.
Secretary: Dr. Francisco Llaurado, Via Layetana 23, Barcelona.

Associacao Paulista de Medicina, Seccao de Pediatrias

President: Dr. Armando de Arruda Sampaio.
First Secretary: Dr. Luis Fontoura y Lauro Machado Oliveira, Caixa Postal 2103, São Paulo, Brazil.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

British Paediatric Association

President: Dr. H. T. Ashby, 13 St. John St., Manchester, England.
Joint Secretary: Prof. Alan Moncrieff, Hospital for Sick Children, Great Ormond St., London W. C. 1.
Place: Windermere.

Chinese Pediatric Society

President: Dr. W. S. Fu, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Secretary: Dr. T. F. Su, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Time: Concurrent with the annual conference of the Chinese Medical Association.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Danish Pediatric Society

President: Prof. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjorup, Dronning Louises Bornehospital, Copenhagen.

Nederlandsche Vereeninging voor Kindergeneeskunde

President: Dr. J. L. Keyzer, 114 St. Josephstr., Tilburg.
Secretary: Dr. H. Reerkink, c/o Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

Royal Society of Medicine, Section for the Study of Diseases in Children

President: Prof. J. M. Smellie, 5 Flat, 8 Bolingbroke Grove, London S. W. 11.
Secretary: Dr. Mary Wilmers; Dr. R. Bonham Carter.
Place: 1 Wimpole St., London W. 1, Time: Fourth Friday of each month, 4:15 p. m.

Schweizerische Gesellschaft fur Padiatrie

President: Prof. Dr. A. Hottinger, Petersplatz 12, Basel.
Secretary: Dr. F. Hauser, Kinderspital, Basel.

Sociedad Boliviana de Pediatria

President: Prof. Dr. Luis V. Sotelo.
Secretary: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Place: Casilla de Correos 12, La Paz, Bolivia.

Sociedad Chilena de Pediatria

President: Mr. Raúl Matte, Santiago, Chile.
General Secretary: Dr. Mariano Latorre, Santiago, Chile.
Place: Medical Society, Santiago, Chile. Time: 7:30 p. m., weekly.

Sociedad Cubana de Pediatria

President: Prof. Augustin Castellanos.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: 9 p. m., last Wednesday of every month.

Sociedad Dominicana de Pediatria

President: Dr. Alberto Peguero, Avenida Bolivar 117, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Jaime Jorge, Lea de Castro 19, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Friday of every month.

Sociedad Ecuatoriana de Pediatria

President: Dr. Alfredo Ceballos Carrión.
Secretary: Dr. Rafael Compte Andrade, P. O. Box 3480, Guayaquil.
Place: Hospital Central. Time: 11:30 a. m., every Friday.

Sociedad Mexicana de Pediatria

President: Dr. Jesus Avarez de los Cobos.
Secretary: Dr. Luis Torregrosa F.
Place: Hospital Infantil. Time: Last Thursday of every month.

Sociedad de Pediatria de Concepcion (Chile)

President: Dr. Raúl Ortega A., Hospital Clínico Regional, Concepción.
Secretary: Dr. Fidel Urrutia, Hospital Clínico Regional, Concepción.

Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., second Tuesday of every month from April to December, inclusive.

SOCIEDAD DE PEDIATRIA DE CORDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Albino F. Dottori, Dean Fumes 2000, Esq. Ocaña (N.) Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Fumes 2000, Córdoba, Argentina.
Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRIA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pastor Oropeza, Caracas.
Secretary: Dr. Guillermo Flores Chacin, Sur 17, No. 26-2, Caracas.
Place: Hospital Municipal de Niños, Caracas. Time: Once a month.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. José Lavalle, Yucatan, Mexico.
Secretary: Dr. Francisco Solís, Yucatan, Mexico.
Place: Hospital del Niño, Yucatan, Mexico.

SOCIETE DE PEDIATRIE DE PARIS

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7e, France.
Secretary: Dr. Maurice Lamy, 94 rue de Varenne, Paris 7e, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. Basil Melle, 89 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.
Secretary-Treasurer: Dr. Seymour Heymann, 17 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Dr. R. Hybbinette, Kommendorsgatan 3, Stockholm.
Secretary: Dr. B. Broman, Eriksbergsgatan 1A, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Héctor C. Bazzano.
Secretary: Dr. José M. Portillo.
Place: Club Medico del Uruguay, Avenida Agraciada 1464 (Piso 13), Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY
SECTION ON PEDIATRICS

Chairman: Dr. Woodruff L. Crawford, 321 W. State St., Rockford, Ill.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.
Place: Atlantic City, N. J. Time: June 6-10, 1949.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. John A. Toomey, City Hospital, 3395 Scranton Rd., Cleveland 9.

Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.

AMERICAN HOSPITAL ASSOCIATION, MASSACHUSETTS HOSPITAL ASSOCIATION
Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

AMERICAN PEDIATRIC SOCIETY
President: Dr. Valjean Cooke, 8700 Argyle Ave., St. Louis.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.
Place: Atlantic City. Time: May 3-5 (?), 1949.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN
President: Dr. P. E. Williams, 193 James St. S., Hamilton, Ontario.
Secretary-Treasurer: Dr. R. L. Denton, 1615 Cedar Ave., Montreal.

SOCIETY FOR PEDIATRIC RESEARCH
President: Dr. Sidney Farber, 300 Longwood Ave., Boston.
Secretary: Dr. Robert Ward, Bellevue Hospital, New York 16.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY
President: Dr. Spencer Snow, 75 S. Main St., Salt Lake City.
Secretary-Treasurer: Dr. Esther Gross, 202 E. South Temple St., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY
President: Dr. Howard W. Brayton, 179 Allyn Street, Hartford 3, Conn.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY
President: Dr. Clarence L. Lyon, 407 Riverside Ave., Spokane 8, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.

NORTHWESTERN PEDIATRIC SOCIETY
President: Dr. Paul Bancroft, 909 Sharp Bldg., Lincoln, Neb.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

ROCKY MOUNTAIN PEDIATRIC SOCIETY
President: Dr. John M. Nelson, 1558 Humboldt St., Denver.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Children's Hospital of the Colorado General Hospital. Time: Monthly from October to June.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS
Chairman: Dr. Carroll M. Pounders, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.
Place: Miami, Fla. Time: October 1948.

STATE

ALABAMA PEDIATRIC SOCIETY
President: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5.
Secretary-Treasurer: Dr. D. B. Monsky, 905 Norman Bridge Rd., Montgomery 6.
Place: Montgomery, Ala. Time: September 1949.

Arizona Pediatric Society

President: Dr. Hugh Thompson Jr., 110 S. Scott St., Tucson, Ariz.
Secretary: Dr. James R. Sickler, Physicians Bldg., Tucson, Ariz.
Place: Phoenix or Tucson. Time: On call.

Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Alice Potter, 1418 Ninth Ave., San Francisco 22.
Secretary: Dr. Carl Erickson, 595 E. Colorado, Pasadena.
Place: Los Angeles. Time: April 1949.

Florida State Pediatric Society

President: Dr. Edgar W. Stephens, 910 Harvey Bldg., West Palm Beach.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

Georgia Pediatric Society

President: Dr. Lee Bivings, 20 Fourth St. N. W., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. F. M. Meyer, 144 Golden Hill St., Bridgeport.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. George L. Drennen, Jacksonville.
Place: Palmer House, Chicago. Time: May 10-12, 1949.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Charlotte Fisk, 1201 Equitable Bldg., Des Moines 9.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.
Place: Des Moines. Time: April 1949.

Louisiana State Pediatric Society

President: Dr. William C. Rivenbank, 1448 Louisiana Ave., New Orleans 15.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.
Place: New Orleans. Time: May 7, 1949.

Medical Society of the State of New York, Pediatric Section

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.
Place: Philadelphia. Time: Oct. 4-7, 1948.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. H. J. Lewis, 2956 Biddle Ave., Wyandotte.
Secretary: Dr. Robert H. Trimby, 122 W. Hillsdale, Lansing.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. Gerald C. O'Neil, 116 S. 49th Ave., Omaha 3.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: Children's Memorial Hospital. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

New Jersey Medical Society, Pediatric Section

Chairman: Dr. Robert E. Jennings, 117 Washington St., East Orange.
Secretary: Dr. Israel J. Wolf, 231 E. 31st St., Paterson.

New Mexico State Pediatric Society

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

North Carolina Pediatric Society

President: Dr. Samuel Ravenel, 371 N. Elm St., Greensboro.
Secretary: Dr. Charles Gay, 1521 Elizabeth Ave., Charlotte.

Northern California Pediatric Society

President: Dr. William C. Deamer, 3 Fifth Ave., San Francisco 18.
Secretary: Dr. A. L. Gleason, 1066 Longridge Rd., Oakland 10.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma State Pediatric Society

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

South Carolina Pediatric Society

President: Dr. B. Owen Ravenel, 95 Rutledge Ave., Charleston 16.
Secretary-Treasurer: Dr. John R. Harvin, 206 N. Sumter St., Sumter.

Tennessee Pediatric Society

President: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Secretary-Treasurer: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Place: Chattanooga. Time: Second Monday in April.

Texas Pediatric Society

President: Dr. Charles B. Alexander, 1716 Nix Professional Bldg., San Antonio 5.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas 4.

Virginia Pediatric Society

President: Dr. Thomas Gibson, 114 W. Boscawen St., Winchester.
Secretary: Dr. E. Berkeley Neal, 303 Washington Ave. S. W., Roanoke.

West Virginia State Medical Society, Section of Pediatrics

President: Dr. Thomas G. Folsom, 1139 Fourth Ave., Huntington.
Secretary: Dr. Warren J. Parsons, 425 Eleventh St., Huntington.

Wisconsin State Medical Society, Section on Pediatrics

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary: Dr. L. M. Simonson, 1001 N. 8th St., Sheboygan.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. John Hart Davis, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Francis F. Silver, 9400 Euclid Ave., Cleveland.

Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. A. L. Chute, 170 St. George St., Toronto, Canada.
Secretary: Dr. John Fletcher, 262 St. Clair St. W., Toronto, Canada.
Place: Academy of Medicine. Tine: 8:30 p. m., third Thursday of each month.

BALTIMORE CITY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore.
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

BRONX PEDIATRIC SOCIETY

President: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Secretary: Dr. William A. Schonfeld, 211 W. 106th St., New York 25.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Harold T. Vogel, 3420-86th St., Jackson Heights, N. Y.
Secretary: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn 16.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

BUFFALO PEDIATRIC SOCIETY

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. T. Wood Clarke, 7 Cottage Place, Utica.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Tuesday of April and October.

CHICAGO PEDIATRIC SOCIETY

President: Dr. John L. Reichert, 1791 Howard St., Chicago 26.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

CINCINNATI PEDIATRIC SOCIETY

President: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Secretary: Dr. William F. Hunting, 6048 Montgomery, Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

DALLAS PEDIATRIC SOCIETY

President: Dr. Guy Hacker, 5711 Goliad St., Dallas.
Secretary-Treasurer: Dr. George R. Branch, 4325 Cole Ave., Dallas.
Place: Children's Hospital of Texas and Bradford Memorial Hospital. Time: 1 p. m., third Saturday and 8:30 p. m., the first Thursday of each month.

DETROIT PEDIATRIC SOCIETY

President: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2.
Secretary: Dr. S. S. Bernstein, 650 Maccabees Bldg., Detroit.
Place: Variable. Time: Five times annually.

HOUSTON PEDIATRIC SOCIETY

President: Dr. Edward O. Fitch, 3720 Fannin St., Houston, Texas.
Secretary: Dr. Thomas J. Donovan, 3506 Sunset Blvd., Houston 5, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., last Tuesday of each month.

KANSAS CITY (MISSOURI) PEDIATRIC SOCIETY

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Hoel Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

KNOXVILLE-OAK RIDGE PEDIATRIC SOCIETY

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

LOS ANGELES COUNTY MEDICAL ASSOCIATION, PEDIATRIC SECTION

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn 16.
Secretary: Dr. Jacob J. Lichterman, 1433 Union St., Brooklyn 13.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. John Washington, 2032 Belmont Rd. N.W., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N.W. Time: Spring and fall.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. C. Barton Etter, 1678 Peach, Memphis 12, Tenn.
Secretary-Treasurer: Dr. Jacob Danciger, 188 S. Bellevue Blvd., Memphis 4, Tenn.
Place: University Center, 4 S. Dunlap. Time: 7 p. m., second Tuesday of every month.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2, Wis.
Secretary-Treasurer: Dr. Katharine Baird, 1411 Wauwatosa Ave., Wauwatosa 13. Wis.
Place: Milwaukee Children's Hospital. Time: Second Wednesday in February, April, June, October and December.

NEW YORK ACADEMY OF MEDICINE, SECTION ON PEDIATRICS

Chairman: Dr. John Dorsey Craig, 120 E. 75th St., New York 21.
Secretary: Dr. Morris Greenberg, 143 W. 87th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. Bertha M. Levy, 717 N. W. 22d St., Oklahoma City 3.
Secretary: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City 3.
Place: Oklahoma Club. Time: On call.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Milton Rapoport, 741 S. 3d St., Philadelphia.
Secretary: Dr. D. Stewart Polk, W. Montgomery Ave., Rosemont, Pa.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. J. A. Gilmartin, 3708 Fifth Ave., Pittsburgh.

Secretary-Treasurer: Dr. C. J. Soecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Municipal Hospital, Pittsburgh. Time: Second Friday in October, December, February and April.

PORTLAND (ORE.) ACADEMY OF PEDIATRICS

President: Dr. Scott Goodnight, 1020 S. W. Taylor St., Portland 5.
Secretary-Treasurer: Dr. Carl G. Ashley, 2455 N. W. Marshall St., Portland 10.
Place: University of Oregon Medical School Library. Time: 8:00 p. m., first Monday of each month from September to June, inclusive.

QUEENS PEDIATRIC SOCIETY

Chairman: Dr. Walter C. A. Steffen, 42-28 Union St., Flushing, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 33-03 Parsons Blvd., Flushing, N. Y.
Place: Forest Hills, N. Y. Time: Third Monday of October, February, April; first Monday of December.

RICHMOND PEDIATRIC SOCIETY

President: Dr. Thomas S. Chalkley, 421 W. Grace St., Richmond 20, Va.
Secretary-Treasurer: Dr. John Paul Jones, 810 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

ROCHESTER PEDIATRIC SOCIETY

President: Dr. Jerome Glaser, 85 San Gabriel Dr., Rochester 10, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. V. E. Hrdlicka, 7424 Cromwell Dr., St. Louis.
Secretary-Treasurer: Dr. Don L. Thurston, 21 Cambridge Court, St. Louis 22.
Place: Hotel Branscome. Time: Second Thursday of each month from October to May, inclusive, 6:30 p. m.

SAN ANTONIO PEDIATRIC SOCIETY

President: Dr. Lucius Hill, 328 Medical Arts Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Bexar County Medical Library. Time: 7:30 p. m., first Tuesday of every month.

SEATTLE PEDIATRIC SOCIETY

President: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle 1.
Secretary: Dr. Jack M. Doctor, 738 Broadway, Seattle 22.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p. m.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. Harry F. Dietrich, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Clement H. Maloney, Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., second Wednesday in January, March, May, September and November.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. Ernest H. Watson, University Hospital, Ann Arbor.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor.
Place: University Hospital, Ann Arbor. Time: Oct. 29-30, 1948.

WESTCHESTER COUNTY MEDICAL SOCIETY, PEDIATRICS SECTION (NEW YORK)

President: Dr. Harry W. Kaessler, 147 Prospect Ave., Mount Vernon, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Fourth Thursday of every other month from September to June (dinner meetings).